SOCIAL COGNITION
IN MESIAL TEMPORAL LOBE EPILEPSY (MTLE)

Thesis
Presented to the Faculty of Arts
of
the University of Zurich
for the degree of Doctor of Philosophy

by
Sarah Dinah Broicher
of Germany

Accepted in the spring/autumn semester 2012 on the recommendation of Prof. Dr. Hennric Jokeit and Prof. Dr. Lutz Jäncke and Prof. Dr. Martin Meyer

(Zurich, 2012)

dedicated to
my family and friends

ACKNOWLEDGEMENT

This doctoral thesis was carried out at the department of neuropsychology at the Swiss Epilepsy Centre in Zurich under supervision of Prof. Dr. rer. nat. Hennric Jokeit, head of department of neuropsychology. Functional MRI measurements were performed at the MR Institute of Radiology of Dominik Huber at Schulthess Clinic.

I would like to express my gratitude to the following:

- Prof. Dr. rer. nat. Hennric Jokeit for his supervision during the three years of my thesis, for sharing his rich experience and immense knowledge in all research and clinical related questions, for his inspiration and support throughout my work, for his critical reviews, his prompt answers to any of my questions, and for guiding me throughout the three years of study
- Prof. Dr. Boris B. Quednow for providing me the possibility to take part in numerous scientific meetings at the Psychiatric University Hospital Zurich and his support and motivation in many ways
- Prof. Dr. Katharina Henke for inspiring me to write a thesis and thus layed the foundation for this work

Each of my three advisors contributed in their own way to the success of this dissertation and to my personal development.

In addition, I am particularly indepted to:

- All patients who participated in this projects. Without their help and cooperation, this work would not have been realised
- Dr. Giorgi Kuchukhidze from the Medical University of Innsbruck and Dr. Lars Frings from the Center of Geriatrics and Gerontology of Freiburg (Germany) for their kind support, encouragement and fruitful cooperation
- Dr. Dominik Huber, Gesa Osterkamp and Theresa Biesold from the Schulthess Clinic in Zurich for the technical support during fMRI measurements and beyond that Gesa Osterkamp for the joy she has given me with her witty sense of humour
- Victoria Reed for meticulously correcting the English in the manuscript

- Many thanks are also due to my colleagues at the Department of Neuropsychology for their kind support and encouragement and numerous cosy and delicious lunch and coffee breaks which were always empowering
- My research colleagues for sharing both success and setbacks and for always being there whenever I needed ready listeners

Finally, I would like to give a special thanks to:

- My friends for their loyal support and encouragement. Without them, I could not have accomplished nearly as much. They all stood by my side from year to year and inspired me in silent ways that resound in endless echoes
- My parents, sisters and my little niece and nephew for their endless love and support help me through any of life's challenges

CONTENT

1 ZUSAMMENFASSUNG

Zahlreiche klinische Studien deuten darauf hin, dass Patienten mit chronischer Epilepsie häufig fehlangepasstes Verhalten und psychiatrische Komorbidiäten aufweisen (Hermann, Seidenberg, & Bell, 2000). Inwiefern diese Fehlanpassungen durch Ängste und Sorgen hinsichtlich der epileptischen Anfälle, die Wahrnehmung von Stigmatisierung und Diskriminierung (z.B. im Arbeitsumfeld) sowie fehlende soziale Unterstützung begründet sind oder auf mögliche Beeinträchtigungen im Bereich sozialer Kognition hindeuten, ist Gegenstand kontroverser Diskussionen (Devinsky & Najjar, 1999; Shackleton, Kasteleijn-Nolst Trenite, de Craen, Vandenbroucke, & Westendorp, 2003).

Aufgaben, welche sozial-kognitive Fähigkeiten verlangen scheinen ein weit distribuiertes neuronales Netzwerk zu aktivieren. Experimente mit bildgebenden Verfahren haben zu Grunde liegende neuronale Prozesse in verschiedenen frontal und temporal gelagerten Hirnregionen lokalisiert (Adolphs, 2003; Gallagher & Frith, 2003; Vollm et al., 2006). Doch obwohl diese Hirnregionen auch bei einer mesialen Temporallappenepilepsie (MTLE) betroffen sind, wurden sozial kognitive Fähigkeiten bei dieser Patientengruppe bisher kaum untersucht (Kirsch, 2006).

Die vorliegende Doktorarbeit hatte zum Ziel, die Frage zu beantworten, inwiefern Patienten mit MTLE gegenüber Patienten mit einer Epilepsie ausserhalb der mesiotemporalen und frontalen Strukturen in ihren sozial-kognitiven Fähigkeiten beeinträchtigt sind. Dabei sollte auch der Frage nachgegangen werden, welche Bedeutung spezifisch der Amygdala zukommt und welche affektiven Funktionen durch diese Struktur und die mit ihr verknüpften Hirnregionen vermittelt werden.

Zu diesem Zweck wurden in einer ersten Studie die Emotionserkennung, das Erkennen von Intentionen und Ansichten anderer (Theory of Mind) sowie die emotional-basierte Entscheidungsfähigkeit mittels einer umfangreichen Testbatterie gut etablierter und empirisch erprobter Testparametern untersucht. MTLE Patienten zeigten gegenüber gesunden Kontrollen sowohl Beeinträchtigungen in der Emotionserkennung in Gesichtern als auch der gesprochenen Sprache, in zahlreichen ToM Tests sowie der Entscheidungsfähigkeit unter Ambiguität und Unsicherheit. MTLE Patienten wiesen gegenüber der Epilepsiekontrollgruppe insbesondere Beeinträchtigungen in der allgemeinen Emotionserkennung auf und zeigten zudem keine adäquate Anpassung des Verhaltens an Rückmeldungen in einem Entscheidungstest. Darüber hinaus unterschied sich die Leistung der Epilepsiekontrollgruppe

weder signifikant von der Leistung der MTLE Patienten noch von jener der gesunden Kontrollen und lag zwischen diesen beiden Gruppen.

Eine Untersuchung von Schacher et al. (2006) deutet darauf hin, dass bei Patienten mit unilateraler MTLE häufig die ipsilaterale Funktion der Amygdala beeinträchtigt ist. Die Bedeutung der Amygdala für die Theory of Mind (ToM) Fähigkeit ist aufgrund der uneindeutigen Befundlage bisher noch nicht geklärt. Somit untersuchten wir in einer zweiten Studie, ob pathologisch asymmetrische amygdaläre fMRI Aktivierungen, die mit einem Lateralisationsindex operationalisiert wurden, mit der Leistung im Recognition of Faux Pas Test in einem Zusammenhang stehen. Patienten mit einer rechtsseitigen MTLE zeigten beeinträchtigte Leistungen im Vergleich zu linksseitigen MTLE Patienten. In Patienten mit rechtsseitiger MTLE korrelierte der fMRT-Lateralisationsindex der ipsilateralen amygdalären Aktivierung signifikant mit der Leistung im Faux Pas Test. Mittels schrittweiser multipler Regressionsanalyse konnte jedoch gezeigt werden, dass der fMRT-Lateralisationsindex, nebst der Seite der Epilepsie, nicht signifikant zur Erklärung der Variation der Leistung im Faux Pas Test beitragen konnte.

Die Amygdala weist Verbindungen mit zahlreichen kortikalen und subkortikalen Arealen auf, einschliesslich Rückprojektionen zum frontalen Kortex. Aufgrund dieser weitreichenden Verknüpfungen, gingen wir in einer dritten Studie der Frage nach, inwiefern sich bei Patienten mit einer Signalminderung in der ipsilateralen Amygdala, funktionelle, modulatorische Einflüsse auf weiter entfernt liegende, aber mit der Amygdala verknüpfte Hirnregionen zeigen. Darüber hinaus untersuchten wir, welche Strukturen innerhalb des Amygdala-Netzwerkes für ToM Leistungen relevant sind. Zur Erfassung funktioneller Konnektivität wurde die nabhängige Komponentenanalyse (Independent Component Analysis, ICA) angewendet, bei der es sich um eine relativ neue, hypothesenfreie, datengetriebene Analysemethode handelt, die dazu dient, unabhängige Signalquellen aus einem Gesamtsignal zu extrahieren und die Konnektivität signifikanter Aktivitätsknoten abzubilden (Calhoun, Adali, Pearlson, & Pekar, 2001). Mittels funktioneller Konnektivitätsanalyse wurde ein Netzwerk identifiziert, welches bei gesunden Kontrollpersonen asymmetrisch organisiert war. Bei MTLE Patienten war diese beobachtete Asymmetrie der Amygdalakonnektivität durch die Lateralisation der Seite des Anfallsbeginns moduliert. Es zeigten sich sowohl bei links- als auch bei rechtsseitigen MTLE Patienten eine verminderte Koaktivierung in linkshemisphärischen temporalen und frontalen Strukturen. Zudem konnten wir zeigen, dass die kontralaterale Integrität eine grössere Rolle für ToM Leistungen zu spielen scheint als die verbleibende ipsilaterale Aktivität. Diese Ergebnisse

wurden als Hinweis auf kompensatorische Aktivierungen kontralateraler mesiotemporaler Strukturen gedeutet.

Eine vierte Studie ging schliesslich der Frage nach, inwiefern die amygdaläre Reaktion im fMRT bei einer dysplastischen Amygdala beeinträchtigt ist. Es zeigte sich, dass eine amygdaläre Läsion (Dysplasie) nicht notwendigerweise mit funktionellen Beeinträchtigungen assoziiert ist, was anhand dreier Patienten mit linksseitiger Amygdaladysplasie gezeigt werden konnte.

Zusammenfassend lassen die vier Studien dieser Dissertation darauf schliessen, dass sozial-kognitive Fähigkeiten bei Patienten mit einer chronischen Epilepsie gegenüber Gesunden beeinträchtigt sind. Auch Patienten mit nicht fokalen Epilepsien, die gleichermassen wie die MTLE Patienten antiepileptische Medikation erhalten, können Schwierigkeiten in der sozialen Kognition aufweisen, dies jedoch deutlich seltener als Patienten mit MTLE. Allein die Chronizität der Erkrankung oder Medikation lassen sich somit für die auftretenden Defizite nicht verantwortlich machen. Die MTLE scheint einen spezifischen Risikofaktor für Defizite in der sozialen Kognition darzustellen, wobei dies vermutlich auf die Beteiligung des fronto-limbischen Systems, einschliesslich der Amygdala, am Krankheitsgeschehen zurückzuführen ist.

2 SUMMARY

Numerous clinical studies have revealed that psychosocial maladjustment is a serious issue for many patients with chronic epilepsies (Hermann et al., 2000). To what extent these maladjustments are caused by social burdens, stigma, and the risk factors of an active epilepsy, and to what extent they are due to dysfunctional social cognition, is still a matter of controversy (Devinsky & Najjar, 1999; Shackleton et al., 2003).

Tasks that demand social cognitive abilities appear to activate a consistent set of brain regions. Experiments using imaging techniques have found underlying neural processes in different frontal and temporal localized brain regions (Adolphs, 2003; Gallagher & Frith, 2003; Vollm et al., 2006). Despite knowledge that these brain regions are frequently affected in patients with mesial temporal lobe epilepsy (MTLE), social-cognitive abilities, such as theory of mind (ToM), have received little attention in this patient group (Kirsch, 2006).

In the present thesis, we conducted four experimental studies to answer the question whether patients with MTLE compared to patients with epilepsies outside the mesiotemporal and frontal structures were specifically impaired in their social-cognitive abilities. Thereby, the questions should be answered which role the amygdala plays in emotional and social function and which affective functions were mediated by the amygdala and its connected brain regions.

Our first study was aimed at investigating emotion recognition, theory of mind, and decision making using a set of tasks that combine behavioural and psychological measures of social and emotional variables. MTLE patients were significantly impaired relative to healthy controls (HC) in all measures of social perception affecting the ability to interpret emotional expressions and feelings from faces and voices and, with one exception, on all advanced tests of reasoning about the mental states of others. MTLE patients were predominantely impaired in their general emotion recognition abilities compared to extra-MTLE patients. In contrast, subjects with extra-MTLE showed no significant impairment in tests of social cognition relative to HC. Performance in the epileptic control group, while not significantly differing from performance in either the MTLE or healthy control group, lay between these two groups on nearly all measures.

Secondly, we wanted to investigate possible effects of functional and structural amygdalar abnormalities on higher-order social behaviour. Thus, patients with mesial temporal lobe epilepsy (MTLE) frequently show ipsilateral amygdalar dysfunctions (Schacher, Haemmerle et al., 2006). However, the role of the amygdala in higher-order social cognition such as ToM

is still under debate. Therefore, our second study aimed at investigating whether the asymmetry ratio of functional magnetic resonance imaging (fMRI) amygdalar activity is related to performance in an advanced ToM task, the recognition of faux pas test. We found lower performances in patients with right-sided MTLE compared to patients with left-sided MTLE in the recognition of faux pas test. In patients with right-sided MTLE, the recognition of faux pas scores correlated with the degree of asymmetry of fMRI activation in the ipsilateral amygdala. However, stepwise multiple regression analysis revealed that the amygdalar asymmetry ratio did not significantly contribute to the explanation of faux pas test performance variability beyond that explained by side of MTLE.

Since the amygdala has extensive connections with many cortical and subcortical areas, including backprojections to the frontal cortex, we further wanted to evaluate wheter ipsilateral amygdalar dysfunction has functional modulatory influences on these remote brain structures. To pursue functional connectivity, we used independent component analysis (ICA) of fMRI data to characterize possible amygdala network alterations that may be caused by ipsilateral amygdala dysfunction. ICA is a relatively new, hypothesis-free, data-driven method which is used to extract independent source signals from an overall signal and that allows one to image connectivity of significant nodes of activity (Calhoun et al., 2001). We furthermore investigated the relationship between activation within the amygdala network and behavioural performance in a ToM task. In healthy controls a hemispheric asymmetry of the amygdala network was present with amygdala co-activation in predominantely left temporolateral and frontal brain strucutes. In MTLE patients the side of pathology modulated the observed asymmetry of amygdala connectivity. In MTLE patients the extent of amygdalar connectivity to the prahippocampal gyrus and insula was related to ToM test performance.

The fourth study was aimed at investigating, whether amygdalar response in fMRI is impaired if it is affected by dysplasia. We found that amygdala lesion (dysplasia) is not necessarily associated with the functional impairment, which was demonstrated in three patients with left-sided dysplasia.

In conclusion, we take our data to suggest that MTLE can be considered as a specific risk factor for the development of social-cognitive deficits. It can be concluded that the chronicity of epilepsy is an important factor in the predisposition of these patients to social-cognitive deficits, but that brain dysfunction can pose an additional hazard, probably related to the involvement of the fronto-limbic system.

ABBREVIATIONS

AED	Antiepileptic drug
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BOLD	Blood-oxygen-level-dependent
CATS	Comprehensive Affect Testing System
EEG	Electroencephalography
FCD	Focal cortical dysplasia
fMRI	Functional magnetic resonance imaging
GLM	General linear model
HC	Healthy controls
HS	Hippocampal sclerosis
IGE	Idiopathic generalized epilepsy
IFG	Inferior frontal gyrus
LI	Lateralization index
LMTLE	Left-sided mesial temporal lobe epilepsy
MRI	Magnetic resonance imaging
MSFG	Medial superior frontal gyrus
MTLE	Mesial temporal lobe epilepsy
MTG	Medial temporal gyrus
PET	Positron emission tomography
pDA	Probable dysplastic amygdala
RMTLE	Right-sided mesial temporal lobe epilepsy
STG	Superior temporal gyrus
STS	Superior temporal sulcus
TLE	Temporal lobe epilepsy

3 GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

This dissertation contains six sections. **Section 1** and **2** give a short summary of the thesis. **Section 3** is the general introduction to the subject of this dissertation. **Section 4** concerns the aims and hypotheses of all four studies. In **section 5.1** emotion recognition and ToM in symptomatic MTLE patients are investigated. Patients with MTLE are compared with patients with extra-MTLE and healthy controls (HC). Also, various aspects of psychopathology and quality of life are assessed to study their contribution to deficits in social cognition. Additionally, other epilepsy related variables are evaluated as potential risk factors for social-cognitive deficits. In **section 5.2** the relationship between the asymmetry ratio of fMRI amygdalar activity and performance in an advanced ToM task, the recognition of faux pas test, is investigated. In **section 5.3** patients with MTLE are compared with HC in functional connectivity of the amygdala. In **section 5.4** the association between structural abnormalities and functional magnetic resonance imaging (fMRI) bold oxygen level dependent (BOLD) response in the amygdala in patients with temporal lobe epilepsy is investigated. In the final section, **section 6**, the results of the studies are summarized and methodological issues and implications for clinical practice and suggestions for future research are discussed.

Social neuroscience is an emerging interdisciplinary field aimed at investigating the fundamentals of human social and emotional behaviour, the quintessence of which is the relationship between brain processes and social interaction. Studies on the impact of neurological, psychiatric, and psychological conditions on human social behaviour contribute to our understanding of the complexity of social interactions and highlight important social and affective symptoms in brain disorders such as epilepsies which continue to be overlooked in clinical practice.

In patients with epilepsy non-social cognitive functions including memory, language and executive functions have been studied for many decades, whereas social cognitive abilities have received little attention (Kirsch, 2006). This is quite astonishing in light of what we know about the remarkable overlap between structures associated with social cognition and anterior brain structures which are frequently affected in patients with epilepsy. The paucity of research becomes more understandable when one considers the lack of readily apparent social deficits in the majority of patients with epilepsies (Phelps & LeDoux, 2005).

Nevertheless, comprehensive clinical studies have revealed that psychosocial maladjustment is a serious problem in many patients with chronic epilepsies (Hermann et al.,

2000). To what extent these maladjustments are caused by social burdens, stigma, and risk factors of active epilepsy, and to what extent they are due to dysfunctional social cognition, remains an open question (Devinsky & Najjar, 1999; Shackleton et al., 2003). However, the fact that psychosocial maladjustment and psychiatric comorbidity are more frequent in certain focal epilepsies compared with other epilepsy syndromes may reflect a specific pathological association (Perini et al., 1996).

In the past, psychiatry and neurology have used different terms and concepts and differed in their diagnostic approaches, research and treatment methods. Their focus converges to some degree within the framework of the modern neurosciences. As such, social and affective neuroscience provides insight into behavioural disorders in patients with epilepsy via new unifying concepts that can be investigated by means of behavioural tests, structural and functional imaging as well as by neuropsychopharmacological interventions. These opportunities allow us to advance our understanding of brain diseases, how they affect behaviour and raise the hope of new and more efficient therapeutic interventions.

3.1 Definition epilepsy and classification

Epilepsy is a worldwide common brain disorder. According to the world health organization (WHO) up to 10% of the general population will suffer from cerebral seizures at least once in their lifetime. Epilepsy is defined as a brain disorder characterised predominantly by recurrent and unpredictable interruptions of normal brain function, called epileptic seizures and by the neurobiologic, cognitive, psychologic, and social consequences of this condition (Fisher et al., 2005). An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal hypersynchronous discharges of cortical neurons. The clinical signs and symptoms of seizures depend on the localization of foci and the extent of propagation of the epileptiform discharge. Seizures can affect consciousness, memory, emotional state, cognition, behaviour and sensory-, motor-, and autonomic functions.

The International League Against Epilepsy (ILAE) proposed an international classification of epilepsy, for both seizure types and epilepsy syndromes to achieve uniform of terminology (1981; 1989). Based on whether the source of the seizure within the brain is localized or distributed, seizures are classified as partial (or focal) or generalized. A seizure is classified as partial when there is evidence of a clinical partial onset, regardless of whether the seizure secondarily generalizes. Partial seizures are further devided on the basis of whether or not consciousness is affected (simple partial seizures vs. complex partial seizues). When a partial seizure spreads within the brain, it is classified as partial seizure with secondarily

generalization. A seizure is considered primary generalized when clinical symptomatology provides no indication of an anatomic localisation and no clinical evidence of focal onset. They can be divided according to the effect on the body into absence, myoclonic, clonic, tonic, tonic-clonic, and atonic seizures. The ictal EEG patterns are usually bilateral and reflect neuronal discharge that is widespread in both hemispheres.

Epilepsy syndromes can be further classified by presumptive cause into idiopathic, symptomatic and cryptogenic. In general, idiopathic (or primary) generalized epilepsy (IGE) is virtually synonymous with genetic epilepsy and means that no underlying cause is apparent other than a possible hereditary predisposition to seizures. When the epilepsy arises from the effects of an epileptic lesion (e.g. metabolic disturbances, cerebral malformations, head injury, infections, brain tumours), the epilepsy syndrome is called symptomatic (or secondary epilepsy). Cryptogenic epilepsy is considered as secondary epilepsy, but the underlying cause has not been identified.

3.1.1 Mesial temporal lobe epilepsy (MTLE)

Mesial temporal lobe epilepsy (MTLE) is the most prevalent focal epilepsy. It is characterized by recurrent seizures that originate from mesial temporal structures, most frequently within the hippocampus. Therefore, hippocampal sclerosis represents the most common pathological substrate in MTLE (Elger, Helmstaedter, & Kurthen, 2004). Neuropsychological examinations often uncover memory impairments which are usually material-specific to the side of ictal onset (Rausch, 1987).

Resective surgery can be highly effective in obtaining seizure freedom in medically intractable patients with MTLE, but bears a significant risk of memory and language impairments. Most candidates for epilepsy surgery are patients with partial epilepsy syndromes refractory to medical treatment. Anterior temporal lobectomy and selective amygdalohippocampectomy are the most common epilepsy surgery and is associated with high success rates (70-80% of patients becoming free of seizures) and low complication rates (Blume, Holloway, & Wiebe, 2001; Clusmann et al., 2002; Siegel, 2004), but bears the risk of side effects such as loss of memory, language disturbances, and emotional alterations, associated with the removal of brain tissue. Such side effects are minimized by careful patient selection, as well as the use of structural and functional imaging techniques (Bonelli et al., 2010; Janszky et al., 2005; Powell et al., 2008) and a battery of neurological and neuropsychological tests that indicate where resection can be made to minimize effects on neurological and cognitive function. Accordingly, a considerable amount of research has been carried out on pre- and postoperative performances on measures of memory, language, and

executive functions (Baxendale, Thompson, Harkness, & Duncan, 2006; Chelune, Naugle, Luders, & Awad, 1991; Helmstaedter & Elger, 1996; Majdan, Sziklas, & Jones-Gotman, 1996).

Moreover, data have been presented in the literature that show an increased rate of psychiatric disturbances in patients with MTLE compared to patients with other types of epilepsy (Hermann et al., 2000; Perini et al., 1996; Quiske, Helmstaedter, Lux, & Elger, 2000). However, it is not clear to what extent psychosocial difficulties are caused by medication (e.g. number and types of medication), psychological and social factors (e.g. fear of seizures, perceived stigma, discrimination, lack of social support) and to what extend they are related to deficits in social cognitive functions.

3.2 Social cognition

Many patients with epilepsy suffer from communication problems and interpersonal difficulties that have a significant bearing on their quality of life. Imaging and lesion studies have identified cerebral networks associated with social cognitive functions which are frequently affected in patients with temporal or frontal lobe epilepsies. Accordingly, recent studies have demonstrated impairments in social cognition in these patient groups using specific tasks involving emotional recognition and theory of mind (Benuzzi et al., 2004; Fowler et al., 2006; Meletti et al., 2003; Schacher, Winkler et al., 2006; Walpole, Isaac, & Reynders, 2008).

Social cognition is a complex and extensive concept that comprises a wide spectrum of sub-processes at different levels of brain functioning (Adolphs, 2006). It includes the perception, encoding, organising and accessing of a variety of relevant social information.

Social cognition is based upon the exchange of signals, whereby the processing of these signals can take place at the automatic and controlled level and is influenced by motivational aspects (Beer & Ochsner, 2006). It is noteworthy that these processes rapidly act in different modalities in parallel and draw on implicit as well as explicit memories. Therefore, it is reasonable to assume that lesions in one or more widely distributed independent components may lead to greater or less severe impairments in social cognition.

Adequate social interactions are a prerequisite for normal human development from an anthropgenetical as well as ontogenetical point of view. Social cognition encompasses any cognitive process that involves conspecifics, either as a group or an individual. It encompasses the ability to build representations about others, oneself, and the relationships between oneself and others, and to apply them flexibly to execute social behaviour (Beer &

Ochsner, 2006). Therefore, the success of social interactions depends upon the ability to understand the cognitive and emotional processes of others (Vollm et al., 2006).

3.2.1 Basal social cognitive processes

Within social cognition one can differentiate between more advanced social cognitive abilities, which require the understanding of complex mental conditions, and more basal processes such as the perception and expression of emotional information.

Processing of emotional information plays an important role in many aspects of cognition (Cacioppo & Gardner, 1999), including decision-making (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994), memory, and attention (Christianson, 1992). Furthermore, understanding other people requires relevant information from different modalities which may provide social information about others including speech, facial expression, prosody, lexical information, gaze direction, gestures and posture. Besides the predominant meaning gleaned from visual information, olfactory, auditory and tactile sensations can also influence processing of social signals (Adolphs, 2006). However, the majority of studies have explored the processing of facial expressions because of longstanding research traditions and well established test materials (Ekman & Friesen, 1976).

Brain damaged patients who exhibit impaired emotional processing, but who are otherwise neuropsychologically intact, show marked deficits in social behaviour and in their interpersonal relationships (Damasio et al., 1994). Emotional agnosia, also called expressive or social emotional agnosia, can be seen as an emotion perception deficit and refers to a form of agnosia in which individuals are unable to perceive facial expressions, body language and intonation, thus making it impossible for them non-verbally to perceive people's emotions and limiting their social interactions. Social-emotional agnosias are commonly observed following amygdala and right cerebral lesions, particularly those involving the temporal lobe (Joseph, 1988).

Although not a form of agnosia in the narrow sense of the word, alexithymia may be difficult to distinguish from, or even co-occur with, emotional agnosia. Whereas emotional agnosia refers to the inability to recognize affect in others (oriented towards others), alexithymia refers to the inability to recognize affect in oneself (oriented towards oneself). Peter Sifneos introduced the term to describe people who appeared to have impairments in understanding, processing, or describing their own emotions (Taylor, 2000).

Despite the importance of emotional expression and processing of emotional information, there are only a few measures available to assess these functions, most of which are not standardised (Borod, 2000) or cross-culturally validated.

More detailed information about measures of basal social cognitive functions is provided in the following sections covering methodological issues and imaging.

3.2.2 Theory of Mind (ToM)

Humans are by far the most talented species in reading the minds of others. This implies that we constantly make assumptions about the intentions and beliefs of others which form the framework of our complex interpretations of human behaviour in daily life. These mentalistic interpretations often seem trivial to us to the point that we fail to perceive them as meaningful, not to mention consider them part of an intuitive psychological theory. Nevertheless they represent a fundamental aspect of social cognition which has been coined theory of mind (ToM) (Premack & Woodruff, 1978). ToM is thought to be the proximate mechanism enabling humans to find their way in complex, collaborative social networks.

The terms empathy, social intelligence, and perspective taking are, along with ToM, related abilities and concepts and were often used as equivalents in the literature as well as in everyday speech. Therefore, social cognition is not equivalent to ToM since there are a number of cognitive abilities which fall within the realm of social cognition which do not involve ToM operations in the narrow sense of the word, e.g. social reasoning and decision making, the recall of knowledge regarding social schemata and moral judgment (Greene & Haidt, 2002).

According to numerous findings, ToM is considered a specific cognitive domain that needs to be delineated from general intelligence and from executive functions. There are many studies in which social cognition has been shown to be dissociable from general intelligence. For example, Baron-Cohen et al. (1997) showed that very high functioning adults (HFA) with autism or Asperger Syndrome (AS), despite being of normal or above average IQ, were nevertheless impaired on a subtle theory of mind test. A further example of this dissociation is seen in Down`s syndrome where intellectual function is impaired, but individuals perform well on theory of mind tasks (Karmiloff-Smith, Klima, Bellugi, Grant, & Baron-Cohen, 1995).

In another study, Baron-Cohen et al. (2001) used a revised version of the “Reading the mind in the eyes Test” (Eyes Test) and administered this test to a group of adults with AS or HFA. Again, there was no significant correlation between IQ and the performance in the Eyes

Test, confirming that this is independent of general (non-social) intelligence. Using the "Mind in the Voice" Task, which extends the aforementioned test into the auditory domain, Rutherford et al. (2002) found that individuals with AS/HFA have difficulty extracting mental state information from vocalizations. Here, too, no significant correlation was found between verbal IQ and performance on the voice task for either the AS/HFA group or the noncollege control group.

Apart from theory of mind, memory, attention, executive functions (including planning of action), motivation and decision making equally contribute to the cognitive and behavioural outputs in social interactions. ToM should be considered a complex neuropsychological function that can be selectively disturbed, but which is correlated with distinct cognitive abilities, in particular executive functions (Rowe, Bullock, Polkey, & Morris, 2001).

Tests which go above and beyond simple attribution performances are also called „higher-order" or „advanced" ToM tests and require the understanding of complex mental states (what does x think or feel?) or also the comprehension of mental states in role-taking activities (e.g. does X also really mean what X says? Why does X behave thus?). The inferences one makes regarding others` mental states include knowledge regarding their thoughts and beliefs ("cognitive ToM component") as well as knowledge and empathic understanding of their emotional states and feelings ("affective ToM component").

3.3 Testing social cognition

The perception and expression of emotional information and ToM abilities have been investigated in numerous studies in a variety of patient groups and healthy persons using a number of experimental paradigms and tests. The following list of selected tests is not intended to be exhaustive, but broadly to cover the most commonly used or representative tests. Short descriptions and behavioural data from a variety of tests are presented below in order to reveal their differences and to highlight recent developments and research perspectives.

3.3.1 Selected tests of basal processes of social cognition

Comprehensive Affect Testing System (CATS)

Test description. Most studies on social cognition have used visual stimuli, but it is clear that real-life social interactions necessarily draw on additional modalities. Audition provides important social signals in addition to language. Accordingly, the intonation of speech –

prosody – can signal various emotions, and is recognised using some of the same structures that we use for recognising facial expressions (Adolphs, Damasio, & Tranel, 2002). Froming et al. (2006) took this issue into account and developed a computerised measurement of visual and auditory emotional processing of the six basic emotions (Comprehensive Affect Testing System, CATS). The CATS consists of thirteen subtests assessing facial identification, emotion matching with and without verbal denotation, emotional tone or prosodic processing with and without verbal denotation, and with conflicting or congruent semantic content.

Behavioural data. The CATS has been administered to patients with Asperger`s syndrome (AS) and comparisons between these patients and healthy controls on CATS subtest results revealed general impairments in the comprehension of facial and prosodic information in the AS group (Froming et al., 2006). Recently, Rocca et al. (2009) applied the CATS to a group of patients with schizophrenia and healthy controls and found that controls performed better on all subtests, the only exception being an affect discrimination task. Data collection is in progress with different groups of patients with brain damage.

3.3.2 Selected tests of theory of mind

Various experimental paradigms exist for evaluating ToM-skills. However a truly theoretically based differentiation of relevant aspects and dimensions of the ToM-construct and its test psychological considerations remain absent.

According to the conceptual classification of a "cognitive" and an "affective" ToM component (with overlaps with empathy), some tests require the attribution of epistemic mental conditions such as knowledge, attention or beliefs while other tests investigate the attribution of affective mental conditions e.g. "feel happy" or "want something" (Stone, Baron-Cohen, Calder, Keane, & Young, 2003). According to Shamhay-Tsoory and Aharon-Peretz (2007), performance on second-order false belief tasks requires cognitive components of ToM while "higher-order" or "advanced ToM tests" such as the faux-pas test (Stone, Baron-Cohen, & Knight, 1998) require both components. The attribution of intention assumes the recognition of whether an action was executed intentionally or accidentally and can be considered as a further type of attribution, although its inclusion under the attribution of epistemic mental conditions seems to be reasonable as well.

Apart from the classification of ToM tests according to their type of attribution, they also differ with regard to the stimulus modality they employ. While some contain verbal material such as stories and subsequently demand adequate language comprehension, complex visual

stimuli are applied in other tests (dynamic and non-dynamic); rarely have verbal and visual material been combined.

Moving Triangles

Test description. Heider and Simmel (1944) conducted an experimental study over 65 years ago that can be seen as the starting point of attribution theory research. In their experiment healthy subjects were asked to interpret a short film sequence (2.5 min) in which three geometric shapes (a big and a small triangle and a circle) move around at different speeds. Another shape in the field is a rectangle which also acts as door that can be opened and closed. All in all, Heider and Simmel's (1944) study contained three experiments. In the first experiment subjects freely described what they saw after watching film sequences twice. In a second experiment, subjects were asked to interpret the movements of the figures as human actions and to answer structured interview questions after presentation of the film. In the third experiment the video was shown in reverse and subjects took part in a short, structured interview. The authors observed that people attributed intentions and desires to moving geometric shapes if these actions are of adequate complexity.

Behavioural data. Klin (2000) developed the Social Attribution Task (SAT), a new cognitive procedure based on Heider and Simmels's cartoon animation and applied it to a group of individuals with autism, with Asperger syndrome (AS), and normally developing adolescents and adults. The SAT is adapted for presentation to developmentally disabled individuals by minimising factors thought to promote ToM task performance but that are absent in real-life social situations. Furthermore, it includes a coding system to examine and quantify different aspects of the subject's social cognitive responses. Both clinical groups showed significant deficits in making social attributions.

Based on the classic Heider and Simmel (1944) paradigm, Abell et al. (2000) aimed to design novel stimuli whose properties of motion would evoke mental state attributions. Protagonists of the new test were two shapes (a big red and a small blue triangle) moving around the screen, which on most trials contained an enclosure. Mental state attributions were restricted to pure movement and interaction in the absence of vocal or facial expression. In their study they presented three different types of animation sequences: random movement in which no interaction occurs (e.g. bouncing), goal-directed (G-D) interactions that elicit attributions of simple actions (e.g. fighting) and ToM interactions that elicit attributions of mental states to the agents (e.g. tricking). The G-D and ToM condition consisted of four animations each, while the random condition had two animations. The computerised

animations were presented to high-functioning children with autism, children with general intellectual impairment, normally developing 8-year olds and adults. The authors found that high-functioning children with autism frequently used inappropriate descriptions when characterising the ToM animations. Castelli et al. (2002) used twelve silent animations, four of each of the three types of animations, and here as well the autism group gave fewer and less accurate descriptions of the ToM animations.

Finally, Heberlein and Adolphs (2004a) used a video of the original Heider and Simmel (1944) film in a single case study and found that a patient who acquired bilateral focal damage during childhood failed to attribute social intent to the moving geometrical objects in the normative manner.

Reading the mind in the Eyes Test

Test description. There are only a few tests which examine ToM skills in adults. So-called "higher-order" or "advanced ToM tests" go far beyond simple attributions and can only be used to study adolescents and adults of normal intelligence, e.g. "Reading the mind in the Eyes test" ("Eyes test") (Baron-Cohen et al., 1997; Baron-Cohen et al., 2001). The subject's task is to choose which of four words best describes what the person in the picture, that shows only a pair of eyes, is thinking or feeling (e.g. terrified, upset, arrogant, annoyed) (Baron-Cohen et al., 2001).

Behavioural data. The Eyes test has enjoyed wide use and has demonstrated reduced test performance in patients with psychiatric diagnoses including autism and AS (Baron-Cohen et al., 1997; Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999; Baron-Cohen et al., 2001) and in patients with schizophrenia (Craig, Hatton, Craig, & Bentall, 2004).

Further, patients with unilateral or bilateral amygdalar lesions (Adolphs, Baron-Cohen, & Tranel, 2002; Stone et al., 2003), with frontotemporal dementia (Gregory et al., 2002) as well as with frontal lobe epilepsy (Farrant et al., 2005) have been found to have impaired performance in the Eyes test. Farrant et al. (2005), however, presume that the discovered deficits in the fvFTD and FLE group are in fact caused by the emotional component rather than ToM itself.

All in all, findings from this widely used test show it to be sensitive for detecting specific ToM impairments in populations that have been found to have deficits in other ToM tests.

Faux Pas Test

Test description. The Recognition of Faux pas Test (Baron-Cohen et al., 1999; Stone et al., 1998) is another ToM test for adults and estimates the ability to recognise and understand a social faux pas. It was designed to evaluate metalizing abilities in individuals with high functioning autism who are able to pass second-order false belief tests. A faux-pas is understood as a statement in which the speaker accidentally offends or insults another person. For example, person "A" complains to person "B" about a wedding present without realising that he is talking to the person from whom he received it. The faux pas test measures several ToM components by including deductions concerning epistemic mental conditions as well as affective mental conditions (Stone et al., 2003; 1998). As verbal materials, in the form of rather complex stories, are used in this task, it makes fairly high verbal demands of the individual.

Behavioural data. Baron-Cohen et al. (1999) administered an age-adapted version of the faux pas test to a group of younger subjects (mean age = 12 years-old) with HFA/AS and found that they had difficulties using mental state knowledge and had difficulties in detecting the faux pas. Unlike the children with HFA/AS in the Baron-Cohen et al. study (1999), adults with AS in Zalla et al.'s study (2009) and the two adolescents with AS in Shamay-Tsoory et al.'s case-study (2002) reported that something awkward or wrong was perpetrated in the faux pas stories; they were generally unable to provide correct justifications in terms of reasons and intentions and failed to attribute emotions to others.

The adult version of this test has also been applied to patients with orbitofrontal and amygdalar lesions (Stone et al., 2003; Stone et al., 1998), TBI (Milders, Fuchs, & Crawford, 2003), patients with mesial temporal lobe epilepsy (Schacher, Winkler et al., 2006), patients with Parkinson disease (Peron et al., 2009), patients with fronto-temporal dementia and patients with Alzheimer disease (Gregory et al., 2002); all of whom had difficulties recognising that a faux pas had been committed.

3.3.3 Self-report questionnaires of psychopathology and quality of life

Saarbrueck Personality Questionnaire (SPF)

The "Saarbrueck Personality Questionnaire" (SPF) is designed to assess empathy. It is translated and validated from the Interpersonal Reactivity Index (IRI) of Davis (1983). We used a 16-item, shortened version of the SPF (Paulus, 2009).

The SPF is a 37-item, 5 point, self-reporting questionnaire. It combines affective and cognitive aspects of empathic reactions and therefore includes the subscales perspective

taking, fantasy, empathic concern, and personal distress. Perspective taking is pointing to the ability to see things from another person's perspective spontaneously; fantasy measures the tendency, to put oneself in the position or role of characters in motion pictures or novels. The subscale empathic concern is constructed to display emotions directed to others as remorse or care of people in trouble, the personal distress subscale though is related to emotions oriented to oneself as concern or indisposition in close interpersonal relationships.

Toronto-Alexithymia Scale (TAS-26)

The Toronto-Alexithymia Scale (TAS-26) assesses various facets of the alexithymia construct. Alexithymia, meaning literally no words for moods, is basically a communication disorder. The construct has been introduced in psychiatry and medical psychology because of a consistent body of clinical and phenomenological observations relating to a particular way of interacting emotionally. The TAS-26 has become one of the widely used measure of the construct and was constructed after a literature review revealed five main content areas thought to reflect the construct (Taylor, 2000; Taylor, Ryan, & Bagby, 1985). We used the German version of the 26-item TAS-26 (Kupfer, 2001).

The TAS-26 uses a 5-point Likert type rating scale from 1 (strongly disagree) to 5 (strongly agree). Apart from a total score, the TAS-26 has three sub-scale scores including: difficulty identifying feelings and distinguishing them from bodily sensations, difficulty describing feelings to others, and externally oriented thinking. According to Taylor et al. (1992), a score equal to or greater than 54 is regarded as indicative for alexithymia.

Beck Depression Inventory (BDI)

Depressive mood was assessed with the Beck Depression Inventory (BDI), a reliably and widely used self-rating questionnaire (Beck, 1984).

The BDI consists of 21 items, with scores that range from 0 to3. A score larger than 12 is considered to indicate a mild form of depressive mood, and a score above 18 is regarded as indicative of clinical depression. Scores were analysed as a continuous variable.

Eysenck Personality Questionnaire (EPQ-RK)

Personality traits were assessed with the German short version of the Eysenck Personality Questionnaire Revised (EPQ-R) (Eysenck & Eysenck, 1976; Ruch, 1999)..

The EPQ-RK comprises of 50 items to be answered in a binary mode ‘yes’/ ‘no’ (Ruch, 1999). The responses define the three personality dimensions of psychoticism, extraversion and neuroticism, complemented by a social desirability scale.

Quality of Life with Epilepsy-31 (QOLIE-31)

The Quality of Life with Epilepsy-31 (QOLIE-31) is the short form of the QOLIE-89, an international, widely used, epilepsy specific questionnaire of quality of life. We applied the German translation of QOLIE-31 which was confirmed as a reliable and valid instrument for assessing aspects of quality of life in patients with epilepsy by Cramer et al. (1998).

The 31 items of the QUOLIE-31 comprised seven subscales (Seizure Worry, Overall Quality of Life, Emotional Well-Being, Energy-Fatigue, Cognitive Functioning, Medication Effects, Social Functioning) and an overall item (Health Status). The raw values were converted to 0–100 scores, whereby higher values reflect better QOL. The total score and the scores for the subscales were calculated according to the QOLIE-31 Scoring Form.

3.4 Imaging of social cognition

Tasks that demand social cognitive abilities appear to activate a consistent set of brain regions. Experiments using imaging techniques have found underlying neural processes in different frontal and temporal localised brain regions (Amodio & Frith, 2006; Stone et al., 1998) including particularly the medial frontal cortex (MFC), inclusive the anterior cingulare cortex (ACC), the superior temporal sulcus (STS) at the temporal parietal junction (TPJ), the temporal poles (TP) and the amygdala.

Medial Frontal Cortex (MFC) and Anterior Cingulate Cortex (ACC). For a better understanding of its role in social cognition, one can functionally divide the MFC into a posterior rostral region (prMFC, associated with cognitive processes) and an anterior rostral region (arMFC, associated with emotional processes), as well as into an orbital region (oMFC, associated with the monitoring of task outcomes). While the prMFC is thought to be engaged in monitoring the value of possible future actions, the oMFC guides behaviour regarding the evaluation of possible consequences. The arMFC appears to be activated by a wide range of social cognition tasks that involve thinking about the psychological attributes of people regardless of whether the person was the self, another person, or whether judgments pertained to dispositions or mental states (Amodio & Frith, 2006). Thus, activations of the arMFC and ACC were found for the perception of oneself as well as one’s own mental conditions (Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; Vogeley et al., 2001) and for the thinking about the mental states of others (Rilling, Sanfey, Aronson, Nystrom, & Cohen,

2004). Based on this knowledge and results which have revealed involvement of the ACC in the control of the attention (Bush, Luu, & Posner, 2000), Gallagher and Frith (Gallagher & Frith, 2003) proposed that the activated parts of the ACC could govern the attention allocated to mental conditions. Thus, the ACC could correspond to the „decoupling“ mechanism which was suggested by Leslie (1994) and which differentiates hypothetical conditions from reality (Frith & Frith, 2003).

Superior Temporal Sulcus (STS). Activation in the area of the STS has consistently and robustly been reported in many studies. It is assumed that the STS represents rather elementary processes involved in a variety of ToM tasks and that the posterior STS is particularly sensitive to biological motion (Allison, Puce, & McCarthy, 2000). Overall, the results point to the participation of the STS in the perception of purposeful actions and their attribution as self-caused or other-caused (Brunet, Sarfati, Hardy-Bayle, & Decety, 2000; Castelli, Happe, Frith, & Frith, 2000).

Temporal Parietal Junction (TPJ). The TPJ appears to be involved in reasoning about the contents of another person’s mind (Saxe & Kanwisher, 2003). In particular, it has been proposed that the right TPJ is selectively involved in representing the beliefs of others (Saxe, Jamal, & Powell, 2006). However, this remains a controversial issue as this region has also consistently been activated during spatial reorienting of visual attention (Mitchell, 2008).

Temporal Pole (TP). The TP may be involved with the retrieval of memory contents, especially autobiographical memories and memories for faces (Gallagher & Frith, 2003). Accordingly, the studies which presumably made only negligible demands on the memory or imagination of the test participant were unable to find any activation in the temporal pole (Gallagher, Cole, & McNeill, 2002; Rilling et al., 2004). Olsen et al. (2007) reviewed the literature in both non-human primates and humans and their findings indicated that the TP has some role in both social and emotional processes including face recognition and ToM.

Amygdala. The amygdala-complex is considered to have a central role in the perception and processing of socially relevant information (Adolphs, 2003; Spezio, Huang, Castelli, & Adolphs, 2007), emotional learning (Phelps et al., 2001) and memory (McGaugh, 2004). The amygdala was shown to react to angry and fearful faces (Adams, Gordon, Baird, Ambady, & Kleck, 2003), be involved in gaze monitoring (Kawashima et al., 1999), and is crucial for the recognition of social emotions . Furthermore, there is converging evidence that amygdala structures and their connecting complex of neural systems are at the core of the ability to interpret the mental states of others (Baron-Cohen et al., 2000; Stone et al., 2003). In their current overview of results from different functional imaging studies of the brain basis of

ToM skills, Carrington and Bailey (Carrington & Bailey, 2009) found the amygdala to be less consistently activated. However, its influence on social and emotional reactions (Adolphs, Schul, & Tranel, 1998) clearly indicates involvement of the amygdala in certain ToM functions.

3.5 Social cognition in temporal lobe epilepsy

Despite knowledge that cerebral networks associated with social cognitive functions are frequently affected in patients suffering from temporal lobe epilepsies, investigations into social cognitive abilities have been scarce (Kirsch, 2006). This paucity of research could be due to the lack of readily apparent social deficits in temporal lobe epilepsy patients (Phelps & LeDoux, 2005).

At the same time, TLE is often associated with behavioural disturbances such as psycho-social maladjustments and psychiatric co-morbidities including depression and social anxiety (Hermann et al., 2000). However, since anxiety and distress related to epileptic seizures and their consequences, stigmatisation and discrimination as well as a lack of social support can be seen as causative variables in the development of psychiatric afflictions (Devinsky & Najjar, 1999; Shackleton et al., 2003), it remains unclear to what extent psychosocial difficulties are caused by these factors and to what extent they are related to deficits in social cognitive functions and, accordingly, to lesions in structures associated with social cognition. The fact that psychosocial difficulties and psychiatric symptoms appear more often in MTLE compared to other chronic epilepsy syndromes (Perini et al., 1996) supports the assumption of an association between MTLE and impairments in social cognition and offers an indication of a possible specific pathology associated with this epilepsy syndrome. Of course, there are other epilepsy syndromes, such as frontal lobe (Farrant et al., 2005) or juvenile myoclonic epilepsy (Piazzini, Turner, Vignoli, Canger, & Canevini, 2008), which may also be at risk of social cognitive impairments, but these have only rarely been investigated and we therefore focus below on TLE.

Basal social cognitive processes

Several studies of basal aspects of social cognition suggest that the recognition of basic emotions in facial expressions is frequently impaired in TLE-patients (Benuzzi et al., 2004; Fowler et al., 2006; Meletti et al., 2003; Shaw et al., 2007; Walpole et al., 2008). In particular, patients with early seizure onset within the right, non-speech dominant, hemisphere showed pronounced difficulties in the recognition of fearful faces (Benuzzi et al., 2004; Meletti et al.,

2003). Also, the early-onset right MTLE-HS patients in Hlobil et al.'s (2008) study were impaired in their ability to recognize fear when compared to other MTLE patients and control subjects, indicating that age of damage is an important factor determining this ability.

Moreover, impairments in the recognition of basic emotions with negative valence have also been reported in temporal lobectomy patients with amygdala damage on the basis of facial- and vocal expressions (Brierley, Medford, Shaw, & David, 2004). The patients in Shaw et al.'s (2007) study who underwent a left anterior temporal lobectomy for medically intractable epilepsy which incorporated the entire amygdala, evaluated fearful facial expressions in a more normative manner. By contrast, in right-sided MTLE patients the operation did not have any effect on the level of impairment.

Theory of mind

Apart from impairments in the recognition of basic emotions (considered to be a prerequisite for a ToM), deficits in emotional memory (Boucsein, Weniger, Mursch, Steinhoff, & Irle, 2001) and in ToM abilities (Schacher, Winkler et al., 2006) have been associated with MTLE.

Abnormalities in higher-order social cognition were directly attributed to MTLE in a study by Schacher et al. (2006). The authors compared patients with MTLE to patients with epilepsy not originating within the MTL and healthy controls in their ability to detect a social faux pas. They used a shortened version of the faux pas test (Stone et al., 2003), consisting of three short prose passages, and found that MTLE patients performed significantly worse in this test than patients with epilepsy other than MTLE (extra MTLE) and healthy controls. This finding was not accounted for by variables such as age, age at seizure onset, duration of epilepsy, text comprehension or IQ and, thus, corroborate earlier findings that ToM abilities are mainly independent of other cognitive functions (Frith & Frith, 2003). Considering that the epilepsy control group exhibited no impairments in the ToM task, the authors concluded that the observed deficit comprised a specific impairment in focal epilepsies with lesions in the ToM-network.

The role of the amygdala in social cognition

The question of the role of the amygdala and the affective functions which it mediates is still under debate (Shaw et al., 2004). The amygdala has been associated with ToM processes in numerous studies (Adolphs, 2003), whereby it appears to be of particular importance in the attribution of affective mental states (Vollm et al., 2006). To detect a social faux pas, as

required in Schacher et al.'s (2006) study, one has to be able to understand the emotional condition of another person. In patients with MTLE, the amygdala are often part of the epileptogenic zone and in about a quarter of patients with hippocampal sclerosis (HS), the ipsilateral amygdala shows volume reduction or even atrophy (Goncalves Pereira et al., 2005; Salmenpera, Kalviainen, Partanen, & Pitkanen, 2001). Furthermore, neuropathological findings in temporal lobe epilepsy patients point to variable degrees of neuronal cell loss and astrogliosis in the amygdala (Aliashkevich et al., 2003; Yilmazer-Hanke et al., 2000).

Disagreement remains as to what degree the amygdala merely supports the development of ToM abilities (Frith & Frith, 2003; Shaw et al., 2004; Tager-Flusberg & Sullivan, 2000) or whether it additionally represents an important part of the neural network which underlies ToM processing abilities (Channon & Crawford, 2000; Happe, Brownell, & Winner, 1999; Sommer, Dohnel, Meinhardt, & Hajak, 2008; Stone et al., 2003). The majority of authors agree with the latter supposition, which receives support in particular from lesion studies that indicate a clear connection between uni- and bilateral lesions of the amygdala and deficits in ToM (Heberlein & Adolphs, 2004b; Stone et al., 2003).

Amygdala fMRI

Apart from these behavioural studies, imaging studies have also been conducted that have detected amygdalar dysfunctions. Using an animated fearful face-paradigm in their fMRI study, Schacher et al. (2006) showed that ipsilateral amygdala functioning is impaired in the majority of patients with mTLE. In contrast, the paradigm resulted in symmetrical bilateral amygdala activation in healthy volunteers.

Bonelli et al. (2009) used a fearful face paradigm to study the role of the amygdala in the processing of emotions in patients with mTLE and to examine whether this may be a potential preoperative predictive marker for emotional disturbances following surgery. Healthy control subjects looking at photographs of fearful faces demonstrated left lateralised amgydala activation, while right-sided TLE patients showed bilateral amygdala activations. Left-sided TLE-patients, however, had significantly reduced activations of either the left or right amygdala in comparison to the control group and the right-sided TLE-patients. During scanning, subjects in Bonelli et al.'s (2009) study were instructed to make judgments of whether photographs of faces were pleasant or unpleasant, a task in which patients with right-sided MTLE were previously shown to have impairments as compared to left-sided MTLE patients and healthy controls (Benuzzi et al., 2004; Meletti et al., 2003). In Bonelli et al.'s (2009) study, the left-sided MTLE patients displayed on average bilaterally reduced fMRI

amygdala reactivity. Inspections of scatter plots revealed, however, considerable interindividual variability in the asymmetry of amygdalar responses, even in patients with left-sided MTLE.

Structure-function analyses have also shown an association between impairments in the recognition of facial expressions, especially of fear (Meletti et al., 2003), and reduced fMRI activity in patients with early onset right-sided TLE (Benuzzi et al., 2004). In addition, an association has been observed between fear recognition deficits and the duration of epilepsy as well as the amount of decrease in amygdalar volume (Houghton et al., 2000; Reynders, Broks, Dickson, Lee, & Turpin, 2005).

In sum, the majority of studies suggest that the degree of impairment and which aspects of social cognition are impaired is influenced by amygdalar pathology in addition to mediating factors such as the age at which and side of which a lesion was acquired, age at seizure onset, the expansion of the symptomatogenic zone as well as the functional deficit zone.

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4 RESEARCH OBJECTIVES

On the basis of the preceding observations, we remain unsure as to whether we should consider deficits in social cognition as defining symptoms of the MTLE syndrome. Since social-cognitive impairments may have a devastating impact on interpersonal relationships, social functioning and quality of life and may promote the occurrence of the frequently reported comorbid symptoms of depression and anxiety, we need to improve and expand our understanding of the relationship between epilepsy and deficits in social cognition. Yet, aspects of social cognition are not often part of the psychiatric or neuropsychological assessment of patients with epilepsies and no comprehensive study exists that investigated emotion recognition, theory of mind, decision-making, psychopathology and quality of life in two well-defined groups of epilepsy patients.

Based on recent findings suggesting that ipsilateral amygdala functioning is impaired in the majority of MTLE patients (Schacher, Haemmerle et al., 2006), a further purpose of our experiments was to investigate possible effects of functional and structural amygdalar abnormalities on higher-order social behaviour.

Therefore, the main objective of this thesis was to study the relationship between MTLE, amygdala functioning and social cognition by investigating the following key objectives:

- Emotion recognition, ToM, decision-making, psychopathology and quality of life in MTLE patients
- Association between ipsilateral amygdalar dysfunction in MTLE, performance in ToM abilities, and lateralization of seizure-onset side
- Association between ipsilateral amygdalar dysfunction in MTLE and functional connectivity of the amygdala with remote temporal and frontal brain areas
- Association between congenital structural abnormalities and fMRI response in the amygdala in patients with TLE

All patients that participate in these studies are recruited in the Swiss Epilepsy Centre in Zurich and the Department of Neurology of Innsbruck Medical University (for the first study). Both clinics are dedicated to the diagnosis, care, counselling and support of patients with epilepsy and related disorders. The referral of patients often entails complex questions concerning the diagnosis, therapy, and psychosocial issues that demand a multidisciplinary

approach. All patients received a thorough neurological, psychiatric and neuropsychological assessment.

4.1 First study: Emotion recognition and theory of mind in symptomatic mesial temporal lobe epilepsy patients (MTLE)

In patients with mesial temporal lobe epilepsy (MTLE), it is common clinical practice to apply memory-, language-, attention- and executive function tests, pointing out cognitive deficits as well as resources, enabling the optimization of the patients' psychosocial and socioeconomic situation. However, none of these tests take account of the fact that patients with MTLE often suffer from communication problems and interpersonal difficulties.

The purpose of this first study was to answer the question whether patients with MTLE are impaired in emotion recognition, theory of mind (ToM), and decicion-making. To address this question we used a set of tasks that combine behavioural and psychological measures of social and emotional variables.

Hypotheses and explorations of the first study:

(1) We hypothesize that patients with MTLE compared to an epilepsy control group and HC are at increased risk for developing social cognitive deficits.

(2) We will explore psychological states and traits, and quality of life of patients with epilepsy.

(3) We will further explore the association of social cognitive performance with epilepsy-related as well as demographic variables.

4.2 Second study: Association between ipsilateral amygdalar dysfunction in mesial temporal lobe epilepsy (MTLE), performance in theory of mind (ToM) abilities, and lateralization of seizure-onset side

Patients with mesial temporal lobe epilepsy (MTLE) frequently show ipsilateral amygdalar dysfunctions as well as deficits in "Theory of Mind" (ToM) tasks. However, the role of the amygdala in higher-order social cognition such as ToM is still under debate. The question was what the amygdala contributes to social cognition.

Therefore, the present study was aimed at investigating whether the asymmetry ratio of functional magnetic resonance imaging (fMRI) amygdalar activity is related to performance in an advanced ToM task, the recognition of faux pas test.

Hypotheses and explorations of the third study:

(1) We hypothesize that amygdala activity induced by fearful face processing is associated with performance in a ToM task.

(2) We will explore the relationship between ToM abilities and the laterality of the epileptogenic zone and amygdala BOLD reactivity.

4.3 Third study: Association between ipsilateral amygdalar dysfunction in MTLE and functional connectivity of the amygdale with remote temporal and frontal brain areas

The amygdala plays a central role in emotion processing and has extensive connections with many cortical and subcortical areas, including backprojections to the frontal cortex. In mesial temporal lobe epilepsy (MTLE) patients with hippocampal sclerosis, reductions in both functional and structural connectivity between hippocampal structures and adjacent brain regions have been reported, whereas little is known about the functional connectivity of the amygdala in unilateral MTLE.

The aim of this study was to evaluate whether ipsilateral amygdala dysfunction has functional modulatory influences on remote temporal, frontal, and parietal brain structures, known to be closely interconnected with the amygdala and to identify their association to theory of mind (ToM) abilities.

Hypotheses of the fourth study:

(1) We hypothesize that MTLE patients show an altered amygdala network in relation to the lateralization of seizure-onset side.

(2) We further hypothesize that left- and right-sided MTLE patients show primarily impaired ipsilateral amygdala connectivity whereas contralateral amygdala connectivity should be less affected.

4.4 Fourth study: Association between structural abnormalities and fMRI response in the amygdala in patients with temporal lobe epilepsy

Functional MRI (fMRI) studies, have demonstrated a major role of amygdalae in processing of emotions by responsivity to fearful facial expressions (Bonelli et al., 2009; Schacher, Haemmerle et al., 2006). In the majority of patients with unilateral temporal lobe epilepsy (TLE) and hippocampal sclerosis (HS), amygdala as well as parahippocampal fMRI

activations were observed contralaterally to the seizure onset side. However, in some patients, dissociation between amygdalar activations and epileptogenic lesion were found. In two patients ipsilateral amygdala activity and reversed asymmetries in parahippocampal activations were observed (Schacher, Haemmerle et al., 2006).

HS is frequently associated with extrahippocampal lesions like focal cortical dysplasia (FCD) Palmini type I, which affects temporal lobe in the majority of cases (Fauser et al., 2006). Few studies addressing the function of FCD demonstrated either its integration in function or a functional "shift" from FCD, which was largely determined by cellular and histochemical properties of FCD. This has been shown mainly in invasive studies related to FCD located in convexital cortical regions (Marusic et al., 2002). This study represents a first effort to investigate non-invasively the functional integrity of amygdala affected by FCD.

The aim of this study was to investigate whether dysplastic amygdalae show an impaired response by functional MRI (fMRI).

Explorations of the second study:

(1) We will explore whether amygdalar response in fMRI is impaired in patients with TLE if it is affected by dysplasia.

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5 ORIGINAL ARTICLES

This doctoral thesis is based on four first authorship articles:

5.1 **Broicher, S.D.**, Kuchukhidze, G., Grunwald, T., Krämer, G., Kurthen, M. and Jokeit, H. (2011). "Tell me how do I feel"a - Emotion recognition and theory of mind in symptomatic mesial temporal lobe epilepsy. *Neuropsychologia,50,118-128.*

5.2 **Broicher, S.D.**, Arter, F., Grunwald, T., Huber, D., Kurthen, M., Krämer, G. and Jokeit, H. Amygdalar fMRI response is related to advanced social cognition in patients with unilateral mesial temporal lobecepilepsy. *Manuscript submitted to Epilepsy and Behavior.*

5.3 **Broicher, S.D.**, Frings, L., Huppertz, H.-J., Grunwald, T., Kurthen, M., Krämer, G. and Jokeit, H. Alterations in functional connectivity of the amygdala in unilateral mesial temporal lobe epilepsy. *Journal of Neurology,*DOI10.1007/s00415-012-6533-3.

5.4 **Broicher, S.**, Kuchukhidze, G., Grunwald, T., Krämer, G., Kurthen, M., Trinka, E. and Jokeit, H. (2010). Association between structural abnormalities and fMRI response in the amygdala in patients with temporal lobe epilepsy. *Seizure,19,*426-431.

5.1 "Tell me how do I feel"a - Emotion recognition and theory of mind in symptomatic mesial temporal lobe epilepsy

Sarah D. Broicher[1], Giorgi Kuchukhidze[2], Thomas Grunwald[1], Günter Krämer[1], Martin Kurthen[1], Hennric Jokeit[1]

[1] Swiss Epilepsy Centre, Zürich, Switzerland

[2] Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

Corresponding author:

Sarah D. Broicher, MSc

Swiss Epilepsy Centre

Bleulerstrasse 60, 8008 Zürich, Switzerland

Tel.: ++41/44/387-6348

Fax: ++41/44/387-6134

e-mail: Sarah.Broicher@swissepi.ch

Key words: social cognition, temporal lobe epilepsy, emotion recognition, theory of mind

Word count: 8272

[a] „Blue Monday", New Order, 1983

ABSTRACT

Specific interictal personality characteristics in epilepsy, sometimes referred to as "Waxmann–Geschwind Syndrome", have been recognised for centuries and extensively described. Despite the persevering clinical impression that patients with mesial temporal lobe epilepsies (MTLE) suffer from problems in communication and interpersonal relations, uncertainties and controversies remain as to the precise origin of these psychosocial difficulties. Here, we investigated social-cognitive and decision-making abilities using a set of tasks that combine behavioural and psychological measures of social and emotional variables to answer the question of whether patients with MTLE are specifically impaired in social cognition compared to both an epilepsy and a healthy control group.

MTLE patients, an epilepsy control group (extra-MTLE; patients with epilepsy, not originating within the frontal or mesial temporal lobe) and healthy controls (HC) were assessed according to their general cognitive status as well as with our Social Cognition Battery, which included tests of basic processes of social cognition, theory of mind, decision making, and various aspects of psychopathology and quality of life.

MTLE patients were significantly impaired compared to HC on most measures of the Social Cognition Battery. MTLE patients were predominantly impaired in general emotion recognition compared to extra-MTLE patients. Performance in the epilepsy control group, although not significantly differing from performance in either the MTLE or healthy control group, lay between these two groups.

MTLE can be considered a significant risk factor for the development of deficits in social cognition beyond weaknesses that might be associated with epilepsy as a stigmatized chronic neurological disorder. The presence of deficits in social cognition may explain various behavioural symptoms that have historically driven concepts such as "epileptic personality" or "interictal personality disorder" and may indicate new routes for therapeutic interventions.

1. Introduction

Standards in neuropsychological diagnostics stem from the pre-imaging period when neuropsychology contributed to the determination of side and location of lesions as well as to the evaluation of functional deficits. For this reason, it was very effective to focus clinical diagnostics on deficits in language and material-specific memory. Nevertheless, problems with social interactions that cannot be explained by deficits related to language, memory or perception had been noticed long ago by epileptologists who coined the terms "interictal personality syndrome" and "Waxmann–Geschwind Syndrome" (Bear & Fedio, 1977; Waxman & Geschwind, 1975). According to this view, a "social abscess" develops more frequently in patients with epilepsy than in patients with other neurological conditions (Guerrant et al., 1962). However, at this time there were neither scientific tools nor concepts to study deficits in social interactions using the paradigms of neuropsychological diagnostics. The very recent development of social neuroscience within the last decade has provided tests and paradigms that may help reveal the underlying deficits responsible for social mal-adaptive behaviour in clinical populations.

Social cognition refers to the capacity to interpret and predict others' behaviour in terms of their beliefs, intentions, feelings, attitudes and perspectives. It enables us to interact in complex social environments and to engage in the activities that we value most, such as family, friendship, love, and cooperation. Accordingly, impairments in social cognition can have a devastating impact on social interactions, interpersonal relationships, employment and experiential activities which are identified as key factors for subjective well being and happiness (Helliwell & Putnam, 2004; Sherman et al., 2008).

Several psychiatric disorders, including autism, Asperger syndrome (Castelli, Frith, Happe, & Frith, 2002; Lind & Bowler, 2009), schizophrenia (Brune, 2005), depression (Zobel et al., 2010), and neurological conditions including uni- or bilateral amygdala lesions (Stone, Baron-Cohen, Calder, Keane, & Young, 2003), traumatic brain injury (McDonald, Flanagan, Rollins, & Kinch, 2003), fronto-temporal dementia, Alzheimer (Gregory et al., 2002), and Parkinson's disease (Peron et al., 2009; Yoshimura, 2007) are accompanied by deficits in social cognition. They all may affect the same brain network by impacting on different nodes of the network that may support the processing of fast automatic, and controlled multimodal information (Lieberman, 2007). Whether social-cognitive deficits also constitute a specific pathophysiological core symptom within epilepsy is still inconclusive, as is the relationship of these deficits to psychopathology.

Mesial temporal lobe epilepsy (MTLE) is the most prevalent focal epilepsy in adults, a chronic neurological condition characterized by clinical manifestations that are a direct reflection of the pathological changes that occur in the inner parts of the temporal cortices (Benbadis, Heriaud, Tatum, & Vale, 2003). Moreover, data have been presented in the literature which show an increased rate of psychiatric disturbances in patients with MTLE compared to patients with other types of epilepsy (Hermann, Seidenberg, & Bell, 2000; Perini et al., 1996; Quiske, Helmstaedter, Lux, & Elger, 2000). However, it is not clear to what extent psychosocial difficulties are caused by medication, psychological and social factors (e.g. fear of seizures, perceived stigma, discrimination, lack of social support) and to what extend they are related to underlying deficits in social cognitive functions caused by brain lesion.

Despite the major involvement of the fronto-limbic system in seizure generation in temporal lobe epilepsy and the recognition of emotions, theory of mind (ToM), and decision-making, few researchers have studied social-cognitive abilities in this patient group (Benuzzi et al., 2004; Bonora et al., 2011; Fowler et al., 2006; Meletti et al., 2009; 2003; Reynders, Broks, Dickson, Lee, & Turpin, 2005; Schacher et al., 2006; Walpole, Isaac, & Reynders, 2008). Research has tended to focus on more basal processes such as the perception and expression of emotional information rather than more advanced social cognitive abilities that require the understanding of complex mental states. One of the first reported studies of higher-order social cognition in epilepsy comes from our laboratory and suggests that patients with MTLE, as compared to patients with epilepsy not originating in the mesio-temporal or frontal lobe and healthy controls, were impaired in their ability to recognize a faux pas, a typical ToM skill (Schacher et al., 2006). Furthermore, few studies have assessed decision-making abilities in MTLE patients (Bonatti et al., 2009; Butman et al., 2007; Delazer et al., 2010a; Delazer et al., 2010b; Labudda et al., 2009). Decision making is a cognitive ability that falls within the realm of social cognition. Patients with MTLE were shown to have difficulties learning from feedback and making decisions under conditions of uncertainty and ambiguity. However, most of these studies failed to include a clinical control group of epilepsy patients who, like patients with MTLE, suffer from a chronic medical condition and receive antiepileptic drug treatment that may influence their psycho-affective states (Schmitz, 2011).

Hence, additional studies of the relationship between type of epilepsy and social-cognitive deficits are needed. However, social cognition is a complex and extensive concept that comprises a wide spectrum of sub-processes at different levels of brain functioning (Adolphs, 2006) and that involve different sensory modalities (verbal-nonverbal, auditory, visual). At a

basic level, the assessment of emotion recognition provides an avenue for examining the ability to interpret simple social signals that are assessed quickly and effortlessly. At a more sophisticated level, an assessment of the capacity to understand conversational inference will reveal difficulties in making abstract judgments about the meanings, beliefs, desires and intentions of a speaker. Therefore, we devised a test battery of social cognition that examines both the ability to interpret emotional expressions from basic paralinguistic and nonverbal information as well as the ability to interpret higher order social cognition from verbal and visual material.

The aim of the present study was to investigate social cognitive functions in patients with MTLE using a variety of tests involving emotion recognition and theory of mind (ToM) in different modalities as well as decision making. As patients with epilepsy often experience psychiatric disturbances, various aspects of psychopathology and quality of life were assessed by means of self-report questionnaires and inventories. The MTLE patients' performance was compared to responses from patients with epilepsy not originating from the frontal or mesial temporal lobes and healthy controls. Furthermore, the association of social cognitive performance with various epilepsy-related variables was studied, as well as the association between social cognitive performance and demographic variables. Finally, the relationship between general psychopathology, quality of life and social cognitive abilities was determined in order to investigate the contribution of psychopathology to deficits in social cognition.

2. Material and methods

2.1 Participants

All patients admitted to the epilepsy monitoring units of the Swiss Epilepsy Centre in Zurich and the Department of Neurology of Innsbruck Medical University were considered for participation in the present study. A total of 42 right-handed adult patients suffering from epilepsies (Innbruck: n=13; Zurich: n=29) qualified and agreed to participate in the study. To be included in this study, a good knowledge of the German language and a confirmed diagnosis of epileptic seizures was required. Patients with a diagnosis of frontal lobe epilepsy were excluded from the study because of the assumed role of frontal lobe function in social cognition. Additional exclusion criteria were an IQ below 75 (representing intellectual impairment) and psychiatric disorders. Adjustment disorders and mild to moderate depression constituted an exception to this rule since it was assumed that they are comorbid symptoms of

temporal lobe epilepsy (Glosser, Zwil, Glosser, O'Connor, & Sperling, 2000; Hermann, Seidenberg, & Jones, 2008). Twenty eight of the 42 patients had a diagnosis of unilateral MTLE (17 left-sided MTLE, 11 right-sided MTLE). MRI scans indicated unilateral hippocampal sclerosis (HS) in 23 patients (12 left-sided, 11 right-sided). Five patients had other lesions within the medial temporal lobe (e.g. parahippocampal gyrus, amygdala). Fourteen patients had idiopathic (*n*=9), cryptogenic (*n*=3), or symptomatic epilepsy (*n*=2) with seizures originating outside the temporal and frontal lobes (extra-MTLE group). The extra-MTLE group served as a clinical control group. Epilepsy patients were classified as MTLE and extra-MTLE on the basis of detailed clinical and neurological examination, typical clinical seizure semiology, continuous interictal and ictal video-EEG monitoring and high-resolution MRI (for clinical data see Supplementary Table S1). Neuropsychological testing revealed no evidence of significant amnesia, agnosia, aphasia, apraxia, alexia, or agraphia in any of the patients. Only patients who had mild to moderate impairments in the domains of attention, executive function, and episodic memory were included in this study.

All patients were treated with first-line antiepileptic drugs (AEDs). Levetiracetam (MTLE, *n*=16; extra-MTLE, *n*=7) and lamotrigine (MTLE, *n*=7; extra-MTLE, *n*=5) were the most frequently used AEDs in both extra-MTLE and MTLE patients. Carbamazepine was also widely prescribed (MTLE, *n*=7) in the MTLE group. Most patients were treated with either AED monotherapy (MTLE, 53.57%; extra-MTLE, 57.14%) or received two drugs in combination (MTLE, 47.43%; extra-MTLE, 42.86%). In line with our inclusion criteria, none of the patients experienced a seizure in the 24-hour period preceding the experimental session.

An additional control group included twenty-nine right-handed healthy participants, who – like the extra-MTLE patients – were matched in age, sex, education and IQ to the MTLE group. Demographic and clinical characteristics of patients with MTLE, extra-MTLE and healthy controls did not differ from each other and are given in Table 1. The study was performed according to the Declaration of Helsinki, approved by the local ethics committees, and all participants gave informed consent.

Table 1
Patient characteristics of MTLE, extra-MTLE patients, and healthy controls.

Variable	Healthy controls (*n* = 29) Mean (SD)	Extra-MTLE patients (*n* = 14) Mean (SD)	MTLE patients (*n* = 28) Mean (SD)	ANOVA or independent samples *t*-test or Kruskal–Wallis Test statistics	*p*
Sex (male; female)	13; 16	10; 4	12; 16	$\chi^2 = 4.30$	.12
Age in years	33.69 (10.94)	33.36 (11.74)	34.43 (13.25)	$F(2,67) = 0.05$	.96
Education in years	14.03 (2.86)	14.04 (2.41)	13.82 (3.56)	$F(2,67) = 0.04$	.96
MWT-B[a] (estimated IQ)	109.34 (10.22)	105.00 (15.35)	101.29 (14.69)	$F(2,67) = 2.68$	.08
Mean age at epilepsy onset in years		18.57 (10.20)	20.21 (11.32)	$t(1,40) = 0.46$	.65
Duration of epilepsy in years		14.79 (11.46)	14.25 (12.47)	$t(1,40) = -0.14$	.89

[a] MWT-B = Mehrfachwahl-Wortschatz-Intelligenz test.

2.2 Procedure

Neuropsychological and psychiatric assessments were carried out after all participants gave written informed consent. All participants performed the multiple-choice vocabulary test (MWT-B) which served an estimate of crystalline verbal intelligence. (Lehrl, Triebig, & Fischer, 1995). The test battery comprised emotion recognition, theory of mind, decision-making, and self-report measures (see below). The entire battery took about 3.5 to 4 hours to complete. Subjects were allowed to request a break at any time during the psychiatric and neuropsychological assessment.

2.3 Emotion Recognition

2.3.1 Comprehensive Affect Testing System (CATS)

CATS aims to measure the perception of facial expressions, prosody, and linguistically presented emotional material and therefore employs the visual and auditory modality of communication (Froming et al., 2006). CATS consists of 13 subtests: 11 emotion tasks and two control tasks assessing facial identification, emotion matching with and without verbal denotation (e.g. in some tasks both emotional faces and the name of the target emotion is displayed on the screen, whereas in other tasks no additional verbal cues are given), emotional tone or prosodic processing with and without verbal denotation (e.g. in some tasks both emotional prosody and the name of the target emotion is displayed on the screen, whereas in other tasks no additional verbal cues are given), and with conflicting or congruent semantic content. Emotional stimuli covered happy, sad, angry, surprised, disgusted, fearful or neutral mood. Instructions and verbal and auditory stimuli for the CATS task were translated by our group into German.

Composite Scales. Each item within a subtest is scored as either correct or incorrect, and items are summed to obtain a raw score for each of the 13 subtests. Data from the 11 emotion related subtests were combined and reduced to five different composite scales: the Simple Facial Scale (Subtests 2 & 5), Complex Facial Scale (Subtests 7, 8, 13), Prosody Scale (Subtests 4, 6, 9), Lexical Scale (Subtests 10), and Cross-Modal Scale (Subtest 11 & 12).

Quotient Scales. Broader scales, based on mode of communication (facial affect and prosody) and emotion per se, are also generated. The Affect Recognition Quotient is obtained by combining the two facial scales; the Prosody Recognition Quotient is identical to the

Prosody Scale, and the Emotion Recognition Quotient is an overarching scale and includes all 11 emotional subtests.

Discrete emotion scales. There are additional scales for each of the six basic emotions that provide information about performance based on type of emotion. Items in the discrete emotion scales test facial affect recognition and are taken from subtests five, 7, 8, and 13.

2.4 Selected tests of theory of mind

2.4.1 Moving Triangles

The Moving Triangles Test aims to measure the extent to which subjects make mental state attributions to dynamic visual stimuli (Abell, Happé, & Frith, 2000; Castelli et al., 2002; Heider & Simmel, 1944). The protagonists of this test were two shapes, a big red triangle and a small blue triangle, that move around the screen. Mental state attributions were restricted to pure movement and interaction in the absence of vocal or facial expression. There were three different types of animation sequences: random movement (RD) in which no interaction occurred (e.g. bouncing), goal-directed (G-D) interactions that elicited attributions of simple actions (e.g. fighting) and theory of mind (ToM) interactions that elicited attributions of mental states to the agents (e.g. tricking). Each sequence lasted between 34 and 45 seconds, and the three types of animations were matched for length.

Verbal descriptions for each of the four examples of the RD, G-D and ToM animation sequences were recorded and coded with respect to three dimensions: ‘intentionality’ (degree of mental state attribution, range 0-5, with absence of mental state language at one extreme and elaborate use of mental state language at the other); ‘appropriateness’ (0-3, with incorrect at one extreme and highly appropriate at the other); and ‘length’ (0-4, ranging from no response to more than four clauses). For more details of materials and scoring procedure see Castelli et al. (2002).

2.4.2 Reading the Mind in the Eyes Test

The “Reading the mind in the Eyes Test” (“Eyes Test”) (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) aims to measure higher-level facial emotion perception where the subject has to infer mental and affective states from social cues of the eye region and thus employ both the visual and verbal modalities. In the Eyes Test the subject’s task is to choose which of four words best describes what the person in the picture is thinking or feeling (e.g. terrified, amused, regretful,

flirtatious). Each picture shows only a pair of eyes from ten different faces (male and female). All faces were standardized to one size (15x10cm), all were black and white, with the same region of the face selected for each photo. All 73 subjects performed a shortened version of the Eyes Test (Baron-Cohen et al., 2001) that comprised ten selected pair of eyes (item numbers 5, 6, 9, 11, 16, 19, 23, 26, 30, and 36). The short version of the Eyes Test was assembled from an independent sample of 20 healthy subjects who completed the full version (unpublished data). In the short version we eliminated those pair of eyes that did not show a sufficient amount of interindividual variability. Reliability analysis between the long and the short version in this sample revealed a sufficient correlation between the two versions (r=.78; p<.001).

The maximum score on this test is 10.

2.4.3 Faux Pas Test

The Recognition of Faux Pas Test (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999; Stein, Corte, Colling, & Whall, 1998; Stone, Baron-Cohen, & Knight, 1998) is an advanced ToM test because it aims to measure mental and affective state attributions from verbal material. This test estimates the ability to recognise and understand a social faux-pas, which is understood as a statement in which the speaker accidentally offends or insults another person. All subjects performed a shortened version of a Faux Pas Test (Stone et al., 2003) that comprised five selected stories. Patients were asked to read each story silently, knowing that they would then be asked questions about the story. The first question concerned the detection and comprehension of the faux pas, while question two, three, and four required the patient to impute the mental state of and attribute emotions to another. Further information related to the test can be found in Schacher et al. (2006).

Data analysis involved the sum of the first four questions, where each question was scored with one point, resulting in a maximum of twenty points for all five stories. Points for the control question were excluded from the total score, but served as an indicator of text comprehension.

2.5 Decision Making

2.5.1 Iowa Gambling Task (IGT)

The Iowa Gambling Task (IGT) aims to measure decision making under initial ambiguity (Bechara, Damasio, Damasio, & Anderson, 1994) and is widely used in research of cognition

and emotion. It tests the ability to choose between favourable card decks with lower gains but also lower risk for losses and unfavourable card decks with higher gains but also higher losses. Participants are presented four decks of cards on a computer screen and are instructed to use the mouse to select cards (overall 100 trials). They were told that each time they choose a card they would win some game money. Occasionally, a card will also have a penalty function and they lose money. Participants were instructed that they could choose cards from any deck and that the goal of the game is to win as much money as possible. Participants were also informed that some decks are better than others and that to win they had to avoid the disadvantageous decks which would lead to losses over the long run and keep selecting from the advantageous decks which would lead to gains. Participants learn the nature of the decks through trial and error.

For each block the number of selections from blocks A and B (disadvantageous) and the number of selections from blocks C and D (advantageous) were counted. Performance on the IGT is scored by a global outcome score (net score) and a score for each of the five consecutive blocks of 20 cards. These scores correspond to the number of cards chosen from the advantageous decks (C+D) minus the number of cards chosen from the disadvantageous decks (A+B). The analysis of the IGT performance by blocks of 20 cards provides information about the learning capacity and strategy used by participants (Bechara, 2001).

2.6 Self-Report-Questionnaires

We further investigated empathy, psychological distress, personality dimensions, empathy and quality of life using the following reliably and widely used self-report measures: (1) the Saarbruecken Personality Questionnaire (SPF) to assess empathy (Davis, 1983); (Paulus, 2009), (2) the Toronto-Alexithymia Scale (TAS-26) to assess various facets of the alexithymia construct (Kupfer, 2001; Taylor, 2000; Taylor, Ryan, & Bagby, 1985), (3) the Beck Depression Inventory (BDI) to assess depressive mood (Beck, 1984), (4) the Eysenck Personality Questionnaire (EPQ-RK) to assess personality traits (Eysenck & Eysenck, 1976; Ruch, 1999), and (5) the Quality of Life with Epilepsy-31 (QOLIE-31) to assess aspects of quality of life in patients with epilepsy (Cramer et al., 1998).

2.7 Statistical analysis

Analyses were carried out using SPSS Version 15. Besides for the overall score of the Beck Depression Inventory and the Moving Triangles Test, we conducted a multivariate analysis of variance (MANOVA) to test the effect of group (MTLE, extra-MTLE, HC) and sex on the test scores of the Social Cognition Test Battery. A separate MANOVA was performed to determine significant differences between groups and sex on the self-report questionnaires. We then applied Bonferroni corrected post-hoc tests.

Performance on the Iowa Gambling Task was separately analysed to explore changes in performance over time. Therefore, IGT data were analysed by a repeated-measures analysis of variance (ANOVA) with blocks (1-5) as the within-subjects factor and group (MTLE patients, extra-MTLE patients, healthy controls) as the between subjects factor. Bonferroni corrected post-hoc tests were then applied. Paired-sample *t*-tests were carried out to inspect differences within groups.

Differences between patient groups on the QOLIE-31 were examined using unpaired *t*-tests. For the BDI and Moving Triangles Test, groups (MTLE, extra-MTLE, healthy controls) were compared by means of Kruskal-Wallis tests. Significant results were further analysed using Mann-Whitney tests.

Additionally, separate MANOVA's for test scores in the Social Cognition Test Battery, and the self-report questionnaires as dependent variables and lateralization (right- vs. left-sided MTLE patients) as an independent variable, were calculated. The confirmatory statistical comparisons of all data across groups were carried out at a significance level set at $p<.05$ (two-tailed).

As the various tests of social cognition and the self-report questionnaires used different response scales, we expressed all data as Z scores in order to accurately compare subscale responses with each other.

2.7.1 Correlation Analysis

Correlations of dependent variables with each other and with demographic variables were tested using Pearson's product-moment correlation.

Within MTLE and extra-MTLE patient groups, we used additional correlation analysis (Pearson Correlation Coefficient) to investigate the relation between age at seizure onset, duration of epilepsy and each test of the Social Cognition Test Battery, the self-report questionnaires and the decision making task.

3. Results

3.1 Demographic and neuropsychological background tasks

Means and standard deviation of socio-demographic, clinical and cognitive variables of healthy controls and patient groups are shown in Table 1. Demographic variables did not differ between the three groups. Therefore, a MANOVA was conducted to investigate group differences on measures of the Social Cognition Test Battery, the self-report questionnaires and the IGT.

3.2 Selected tests of emotion recognition and theory of mind

A MANOVA comparing the three groups on all tests of the Social Cognition Test Battery as a whole revealed neither a significant main effect for group, based on Pillai's Trace, $F(32,88)=1.13$, $p=.32$, nor a significant main effect for gender, $F(16,43)=.54$, $p=.91$, nor for group x gender interaction, $F(32,88)=$, $p=.76$. We report effects of group for single dependent variables below. Sample sizes vary slightly by subgroup due to missing values.

3.2.1 CATS

All patients (MTLE: $n=24$, extra-MTLE: $n=14$) and HC ($n=28$) showed normal levels of effort, indicated by validity scores within the normal range. Less than 10% of our sample obtained combined scores of less than 31, paralleling the results of Froming et al. (Froming et al., 2006).

Quotient Scales. Comparing the three groups on the quotient scales revealed a significant main effect of group for all three quotients, namely the Affect, Prosody, and Emotion Recognition Quotient. Post hoc analysis revealed that MTLE patients performed significantly worse compared to HC on all quotient scales (ARQ, $p=.006$; PRQ, $p<.001$; ERQ, $p<.001$) as well as compared to extra-MTLE patients on the ERQ ($p=.02$). Extra-MTLE patients and HC did not differ in terms of the quotient scales (all $p>.05$). (see Table 2 and Fig. 1).

Composite Scales. Comparing the three groups on the composite scales showed a significant main effect of group for the complex facial and prosody scale (see Table 2). Post hoc tests showed that MTLE patients were impaired compared to HC ($p=.01$), but not compared to extra-MTLE patients ($p=.07$), in complex facial emotion recognition. Also prosody recognition was impaired in MTLE patients compared to HC (Prosody Scale,

p=.003), but not compared to extra-MTLE patients (*p*=.15). Extra-MTLE patients and HC did not differ in terms of the composite scales (all p>.05). There were no significant differences between groups with regard to the simple facial, lexical, and cross modal scale (see Table 2 and Fig. 1).

Discrete emotion scales. With regard to the specific type of emotion, there was a significant main effect of group for recognition of fear, sadness, and disgust (see Table 2), with post hoc tests showing that MTLE patients compared to HC were specifically impaired on the emotion type fear (*p*=.005), and disgust (*p*=.04) (see Table 2 and Fig. 1)

Correlation Analysis. With regard to CATS quotients, ARQ (*r*=−.287, *p*<.05), PRQ (*r* =−.449, *p*<.001), and ERQ (*r*=−.410, *p*<.001) correlated with age, PRQ (*r*=.266, *p*<.05) and ERQ (*r*=.298, *p*=.02) with verbal IQ. These results indicate a decline in visual and auditory emotion recognition performance with the person's age. Additionally, lower performance in general emotion recognition performance, particularly in auditory emotion recognition abilities, were associated with reduced verbal IQ. ERQ (*r*=−.316, *p*<.01) correlated with years of education, indicating that poorer general emotion recognition performance is associated with fewer years of education.

Within MTLE and extra-MTLE patients, there were no significant correlations between quotients and clinical variables including duration of epilepsy and age at epilepsy onset as well as between composite scales and the same clinical variables.

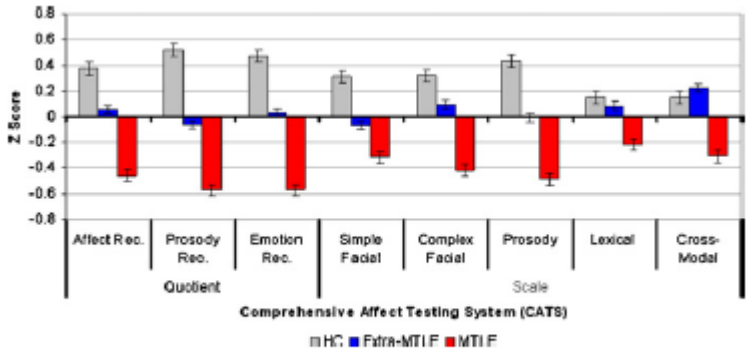

Fig. 1. Performance of MTLE patients, extra-MTLE patients, and healthy controls on the CATS quotients and CATS scales expressed as *Z* scores.

Table 2
Results for each group on the comprehensive affect testing system (CATS).

Variable	Healthy controls Mean (SD)	Extra-MTLE patients Mean (SD)	MTLE patients Mean (SD)	MANOVA (and post hoc Bonferroni) (df = 2, 63) F	p	Bonferroni	Effect size
Affect Recognition Quotient	50.54 (4.23)	48.86 (6.27)	46.12 (5.21)	5.32	.008**	MTLE** < HC	.16
Prosody Recognition Quotient	26.11 (2.42)	24.29 (3.34)	22.67 (2.90)	10.02	.001**	MTLE*** < HC	.26
Emotion Recognition Quotient	105.68 (7.96)	100.86 (13.32)	94.29 (9.60)	9.73	.001**	MTLE < HC***, extra-MTLE*	.25
Simple Facial Scale (2, 5)	16.25 (1.82)	15.64 (1.34)	15.25 (1.36)	2.95	.06		.09
Complex Facial Scale (7, 8, 13)	34.29 (3.78)	33.21 (5.18)	30.88 (4.70)	4.33	.02*	MTLE** < HC	.13
Prosody Scale (4, 6, 9)	25.71 (3.08)	24.29 (3.34)	22.67 (2.90)	6.35	.003**	MTLE** < HC	.18
Lexical Scale (10)	9.14 (4.31)	8.93 (1.82)	7.92 (2.62)	0.94	.40		.03
Cross Modal Scale (10, 12)	19.07 (2.93)	19.29 (3.10)	17.54 (3.75)	1.88	.16		.06
Discrete Emotion Scales							
Surprised	6.57 (1.10)	6.57 (1.22)	6.46 (1.10)	0.17	.85		.01
Fearful	7.45 (0.98)	7.14 (1.29)	6.46 (1.18)	5.55	.006**	MTLE** < HC	.16
Sad	7.04 (1.26)	7.07 (1.33)	6.08 (1.72)	3.84	.04*		.10
Angry	5.14 (1.76)	5.14 (1.75)	4.79 (1.56)	0.30	.74		.01
Disgusted	6.63 (2.02)	5.64 (1.95)	5.25 (1.67)	3.16	.05*	MTLE* < HC	.10

* MANOVA (and post hoc Bonferroni) is significant at the $p < .05$ level (two-tailed).
** MANOVA (and post hoc Bonferroni) is significant at the $p < .01$ level (two-tailed).
*** MANOVA (and post hoc Bonferroni) is significant at the $p < .001$ level (two-tailed).

3.2.2 Moving Triangles

As shown in Table 3, in all three groups (MTLE: *n*=22, extra-MTLE: *n*=13, HC: *n*=28) the ToM animations evoked more mental state attribution than did goal-directed animations, which in turn evoked more such descriptions than random animations.

Attribution of Intentionality. A Kruskal-Wallis test demonstrated a significant group difference in the degree of mental state attribution, with pairwise Mann-Whitney comparisons showing that the MTLE group attributed less intentionality to the characters' behaviour relative to the HC during ToM animations (*Z*=-2.99, *p*=.003) and goal-directed animations (*Z*=-2.95, *p*=.003), whereas no effect of group was found during random animations (see Table 3 and Fig. 2).

Appropriateness of the Explanations. There was another significant group difference in the appropriateness of the explanations given to the goal-directed animation type, with the MTLE group giving less appropriate explanations than the HC (Z=6.27, p=.04). Again there was no effect of group with regard to appropriateness during random or ToM animations (Table 3 and Fig. 2).

Length of the Descriptions. The length of the descriptions did not differ between groups (see Table 3).

Correlation Analysis: Across ToM animations, attributions of intentionality correlated with verbal IQ (*r* =.434, *p*<.01) and years of education (*r* =.374, *p*<.01). In addition, the appropriateness of the explanations given to the ToM animations correlated with verbal IQ (*r* =.301, *p*<.05). A significant negative correlation was found between attributions of intentionality and duration of epilepsy (*r*=-.427, *p*<.05).

In summary, these results indicate that regardless of group membership, those with less education and lower verbal IQ performed worse on this task. Significantly poorer task performance was also associated with MTLE patients with longer duration of epilepsy.

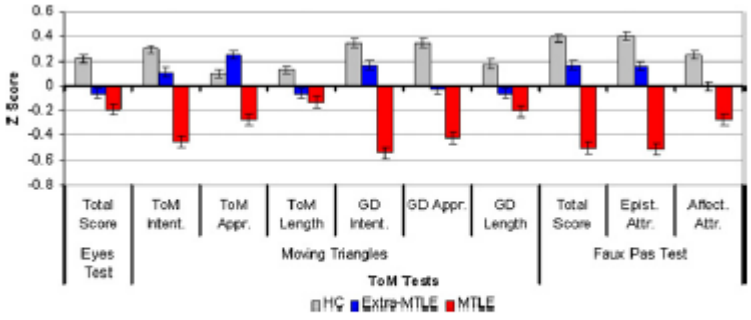

Fig. 2. Performance of MTLE patients, extra-MTLE patients, and healthy controls on different ToM tests (Eyes Test, Moving Triangles Test, Faux Pas Test) expressed as *Z* scores.

3.2.3 Eyes Test

Comparing the three groups (MTLE: *n*=28, extra-MTLE: *n*=14, HC: *n*=29) on the shortened version of the Eyes Test revealed no significant main effect of group (see Table 3).

Correlation Analysis: Performance in the Eyes Test was not correlated with age, years of education, or verbal IQ (all $p>.05$). Within both patient samples, no significant correlations were found between performance on the eyes task and age at epilepsy onset or duration of epilepsy (all $p>.05$).

3.2.4 Faux Pas Test

All participants in the three groups (MTLE: *n*=27, extra-MTLE: *n*=13, HC: *n*=29) correctly answered the control question. There was a significant main effect of group on the total number of correct detections and epistemic attributions, but not in affective attributions (see Table 3). Errors in the epistemic attributions all involved assuming that the faux pas had been made intentionally with the aim of upsetting the other protagonist in the vignette. Bonferroni post hoc tests revealed significantly impaired overall performance ($p=.02$) and epistemic attributions ($p=.02$) for the MTLE patients compared to HC, but not compared to the extra-MTLE group (all $p>.05$). Also, extra-MTLE patients and HC did not differ with regard to faux pas test performance (see Table 3 and Fig. 2).

Correlation Analysis. Performance on the Faux Pas Test was not correlated with age, years of education, or verbal IQ (all $p>.05$). Across epilepsy patient groups, there were no

significant correlations between Faux Pas Test performance and the clinical variables age at epilepsy onset and duration of epilepsy (all $p>.05$).

Table 3
Results for each group on Theory of Mind Tests (ToM).

Variable	Healthy controls Mean (SD)	Extra-MTLE patients Mean (SD)	MTLE patients Mean (SD)	MANOVA (and post hoc Bonferroni) or Kruskal–Wallis (and pairwise Mann–Whitney) Test statistics	p	Bonferroni or Mann–Whitney	Effect size
Eyes Test, total score (0–10)	7.52 (1.56)	7.07 (1.33)	6.86 (1.76)	$F(2/68) = 73$	.48		.03
Moving Triangles, ToM intentionality (0–5)	3.97 (0.70)	3.81 (0.77)	3.34 (0.96)	$\chi^2 = 8.94$	.01*	MTLE** < HC	
Moving Triangles, ToM appropriateness (0–3)	2.56 (0.45)	2.71 (0.51)	2.39 (0.52)	$\chi^2 = 1.97$	.37		
Moving Triangles, ToM length (0–4)	3.46 (0.65)	3.35 (0.57)	3.31 (0.63)	$\chi^2 = 0.66$	.72		
Moving Triangles, goal-directed intentionality (0–5)	2.29 (0.47)	2.20 (0.52)	1.82 (0.48)	$\chi^2 = 9.12$	.01*	MTLE** < HC	
Moving Triangles, goal-directed appropriateness (0–3)	2.71 (0.26)	2.65 (0.48)	2.44 (0.41)	$\chi^2 = 6.27$	.05*	MTLE* < HC	
Moving Triangles, goal-directed length (0–4)	2.57 (0.83)	2.4 (0.45)	2.31 (0.60)	$\chi^2 = 0.923$	.63		
Moving Triangles, random intentionality (0–5)	0.38 (0.45)	0.15 (0.22)	0.42 (0.62)	$\chi^2 = 1.89$	.39		
Moving Triangles, random appropriateness (0–3)	2.9 (0.16)	2.98 (0.62)	2.77 (0.37)	$\chi^2 = 1.16$	.56		
Moving Triangles, random length (0–4)	2.11 (0.94)	1.52 (0.50)	1.70 (0.66)	$\chi^2 = 5.57$	.06		
Faux Pas Test, total score (0–20)	18.64 (1.88)	18.08 (2.17)	16.39 (2.75)	$F(2/66) = 4.05$	.02*	MTLE* < HC	.12
Faux Pas Test, affective attributions (0–5)	4.69 (0.63)	4.54 (0.66)	4.37 (0.33)	$F(2/66) = 1.16$	.32		.04
Faux Pas Test epistemic attributions (0–5)	4.29 (0.93)	4.00 (1.02)	3.17 (1.38)	$F(2/66) = 3.91$	.03*	MTLE* < HC	.12

Sample sizes vary slightly by subgroup due to missing values.
* MANOVA (and post hoc Bonferroni) or Kruskal–Wallis (and pairwise Mann–Whitney) is significant at the $p < .05$ level (two-tailed).
** Kruskal–Wallis (and pairwise Mann–Whitney) is significant at the $p < .01$ level (two-tailed).

3.3 Decision making

3.3.1 Iowa Gambling Task (IGT)

Data for 25 HC, 14 extra-MTLE patients, and 19 MTLE patients were available for analysis. Performance of the experimental groups on the IGT is shown in Fig. C.1.

An ANOVA of the IGT global outcome score across all groups showed a significant main effect of the factor group, $F(2,50)=5.74$, $p=.006$. Post-hoc Bonferroni tests revealed that the MTLE patients performed significantly worse compared to HC ($p=.02$), but not compared to extra-MTLE patients ($p=1.00$). Extra-MTLE patients and HC also differed in terms of the global outcome score ($p=.03$).

A repeated-measures ANOVA with blocks (1–5) as the within-subjects factor and group (MTLE, extra-MTLE, healthy controls) as the between-subjects factor was carried out on the IGT net scores. The main effect of block, $F(4,220)=13.92$, $p<.001$, as well as the main effect of group, $F(2,55)=6.67$, $p=.003$ was significant, reflecting the strategy shift across blocks and indicating different preferences of decks in total between the groups. The interaction of both factors was not significant, $F(8,220)=1.14$, $p=.34$. Post-hoc Bonferroni tests showed that MTLE patients performed significantly worse compared to HC ($p=.007$), but not compared to extra-MTLE patients ($p=1.00$). Extra-MTLE patients and HC also differed in terms of the net score ($p=.02$).

When only comparing performance of the first to the fifth block, paired samples *t*-tests revealed that the frequency of advantageous selections markedly increased over the task for

HC (block 1 vs. block 5: $t(24)=-6.80$, $p<.001$) and extra-MTLE patients, $t(13)=-3.23$, $p=.007$, but did not significantly increase for MTLE patients, $t(18)=-1.65$, $p=.12$.

Correlation Analysis. Performance on the IGT was not correlated with age, years of education, or verbal IQ (all p>.05). Within the MTLE group, the global outcome score of the IGT was correlated with duration of epilepsy ($r=-.53$, $p<.05$), indicating that a longer duration of epilepsy was associated with impaired decision-making performance.

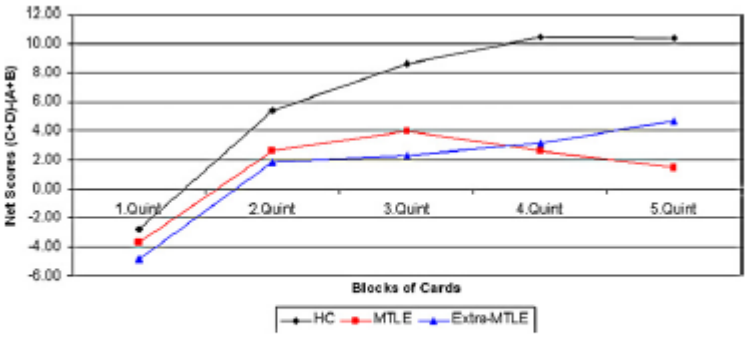

Fig. 3. Performance of MTLE patients, extra-MTLE patients, and healthy controls on the Iowa Gambling Task (Bechara et al., 2001) as scored by a global outcome score (net score) and a score for each of the consecutive blocks (1–5) of 20 cards (means ± standard error of means).

3.4 Self-Report Questionnaires

We used MANOVA to investigate group x gender differences on the self-report questionnaires. A significant main effect for group, based on Pillai's Trace, $F(24,102)=1.82$, $p=.02$, but no significant main effect for gender, $F(12,50)=1.64$, $p=.12$, or for gender x group interaction, $F(12,50)=1.28$, $p=.27$, was observed.

Across patient groups, no significant correlations between any self-report questionnaire and the clinical variables age at epilepsy onset, or duration of epilepsy were found (all p>.05). Below we report the effects of group on single dependent variables. Sample sizes vary slightly by subgroup due to missing values.

3.4.1 Saarbruecken Personality Questionnaire (SPF)

Groups (MTLE: $n=27$, extra-MTLE: $n=13$, HC: $n=29$) differed neither on the total score of the SPF, nor on the subscales fantasy, empathic concern and perspective taking (see Supplementary Table S2).

3.4.2 Toronto-Alexithymia Scale (TAS-26)

The majority of MTLE (22/28; 79%) and extra-MTLE patients (13/14; 93%) and all subjects in the healthy control group (28/28) had TAS scores below the cut-off of 54, which would be indicative for alexithymia. No significant group effect emerged for the subscales difficulty communicating emotions and externally oriented thinking (Table S2). A significant effect of group was found for the mean TAS score and the difficulty identifying emotions subscale of the TAS, with post hoc comparisons revealing that the MTLE group was overall more alexithymic (p=.005), and had significantly more difficulty in identifying (p=.001) and communicating emotions (p=.05) compared to HC (see Supplementary Table S2).

3.4.3 Beck Depression Inventory (BDI)

In all three groups the mean score for the BDI was within the normal range of HC (Beck, 1979) (for mean depression scores on the BDI see Supplementary Table S2). No subjects within the healthy control group had a BDI score above the cut-off of 12 (indicative for a mild form of depressive mood). The majority of MTLE (16/23; 70%) and extra-MTLE patients (10/13; 80%) had BDI scores lying under the cut-off of 12. Seven out of 23 (30%) in the MTLE group and three out of 13 (25%) in the extra-MTLE group had a score above 12 and below 19, indicating mild to moderate depressive mood, and none had a score above 18, indicating a clinical depression.

Kruskal-Wallis test revealed significant group difference in the overall score, with pairwise Mann-Whitney comparisons showing that the MTLE group (Z=-5.11, p<.001) and the extra-MTLE group (Z=-2.99, p=.003) had more depressive symptoms relative to HC (see Supplementary Table S2).

3.4.4 Eysenck Personality Questionnaire (EPQ-RK)

Comparisons of the three groups (MTLE: n=28, extra-MTLE: n=12, HC: n=28) on the EPQ-RK revealed a significant main effect of group for the subscale Neuroticism, whereas groups did not differ in the other personality domains Extraversion and Psychoticism, or with regard to Social Conformity. Post hoc analysis revealed that MTLE patients compared to HC (p=.01), but not compared to extra-MTLE patients (p=.09), described themselves as distinctly more neurotic (see Supplementary Table S2).

3.4.5 Quality of Life with Epilepsy-31 (QOLIE-31)

T-Tests that examined mean differences between MTLE (MTLE: *n*=28) and extra-MTLE patients (MTLE: *n*=14) in quality of life indicated that MTLE patients had a lower subjective quality of life compared to extra-MTLE patients as indicated by a lower Overall Score as well as lower scores on the subscales Overall Quality of Life and Social Functioning. With respect to the QOLIE Emotional Well Being subscale score, no significant differences were found between the two groups (see Supplementary Table S2).

3.5 Correlations between behavioural measures of social cognition

Pearson's product-moment correlations between the emotion recognition, the theory of mind, and the decision-making task revealed that facial emotion recognition (ARQ) was highly correlated with emotion recognition from prosody (PRQ) as well as with general emotion recognition (ERQ), which in turn was also highly correlated with PRQ. Emotion recognition from a face and prosody were also highly correlated with the extent of intentional attributions that had been made as well as with the appropriateness of the explanations that had been given for ToM animations. It also appears that, independent of the channel of communication, emotion recognition was related to the IGT global outcome score. Whereas the Eyes and Faux Pas Test were not correlated with emotion recognition, they were found to correlate with each other.

3.6 Correlations between behavioural measures of social cognition and subjective measures of psychological distress, personality dimensions, empathy and quality of life

Across both epilepsy groups, Beck Depression Inventory (BDI) scores did not correlate with emotion recognition, neither from face nor from prosody, nor with any other measures of theory of mind or the decision-making task (all Spearman's $p>.05$). Within all groups, a lack of correlation between behavioural and subjective measures was also observed (all $p>.05$). Only when both epilepsy patient groups were combined was QOLIE Social Functioning correlated with emotion recognition from prosody ($r=.43$, $p=.008$), whereas the lack of association between all other measures remained (all $p>.05$).

3.7 Effect of Side of MTLE

Right- and left-sided MTLE did not differ with regard to demographic variables such as sex, age, verbal IQ, years of education, age at epilepsy onset and duration of epilepsy (all $p>.05$).

We analyzed the MTLE group in more detail by first analyzing the influence of the side of epilepsy within the MTLE group on tests from the Social Cognition Test Battery as well as the self-report questionnaires by applying separate MANOVA's with the fixed factor side of epilepsy.

On the Social Cognition Test Battery, a significant effect of the factor group was found only for the CATS emotion type fear. Patients with right-sided MTLE performed worse on CATS emotion type fear compared to left-sided MTLE patients, $F(1, 20)=5.42$; $p=.03$, $eta^2=0.21$. No effect of the factor side of epilepsy was found on any of the tests of the self-report questionnaires (all $p>.05$).

For the IGT, repeated-measures ANOVA's were performed for right- and left-sided MTLE groups as well as for men and women on all relevant parameters. No significant group effects were found in these analyses.

4. Discussion

4.1 Main findings

In the present study we assessed emotion recognition, theory of mind, decision making, psychological states and traits, and quality of life in a group of patients with MTLE.

The study demonstrated deficits in subjects with MTLE compared to HC in all measures of social perception affecting the ability to interpret emotional expressions and feelings from faces and voices and, with one exception, on all advanced tests of reasoning about the mental states of others. MTLE patients were predominantly impaired in their general emotion recognition abilities compared to extra-MTLE patients. In contrast, subjects with extra-MTLE showed no significant impairment in tests of social cognition relative to HC. Their performance, however, also did not differ from the performance of the MTLE group and lay between these two groups on nearly all measures. It is reasonable to assume that, independent of the site of seizure onset in the extra-MTLE group, fronto-limbic structures might be affected due to frequent propagation of epileptic brain electric activity from posterior to

anterior areas. This also implies that patients with other epilepsy syndromes, who equally were treated with antiepileptic drugs (AEDs), might be at risk of suffering from difficulties in social-cognitive abilities, albeit to a lesser degree than MTLE patients. Another possible explanation for the absence of significant differences between the two patient groups is the heterogenous composition of the extra-MTLE group with patients affected by different epilepsy syndromes which emphasizes the need for more homogenous control groups. Overall our results support the claim that MTLE is a risk factor for deficits in social cognition beyond weaknesses that are associated with an epileptic disorder in general.

4.2 Emotion recognition from faces and prosody

We revealed that patients with MTLE, as compared to HC, are impaired in complex facial and auditory emotion processing, but not in lexical emotion recognition. This is in accordance with a recent finding suggesting that the basic emotion recognition impairment in MTLE patients is not dependent on the sensory modality through which emotional material is perceived (Bonora et al., 2011). Moreover, impairments in the recognition of basic emotions with negative valence have also been reported in temporal lobectomy patients with amygdala damage on the basis of facial and vocal expressions (Brierley, Medford, Shaw, & David, 2004). By contrast, two other studies failed to find differences in recognizing emotional prosody in a small group of patients after temporal lobectomy (Adolphs, Tranel, & Damasio, 2001) and in a group of patients with MTLE and asymmetrical amygdala damage (Fowler et al., 2006). However, these negative results could be due to small sample sizes, item and task characteristics and different clinical patient characteristics. Rocca et al. (2009), who applied the CATS to a group of patients with schizophrenia and healthy controls, found that controls performed better on all subtests with the exception of an affect discrimination task. By contrast, analysis of component scales revealed that MTLE patients as compared to HC performed worse on the complex facial and prosody scale, whereas performance on the simple facial, lexical and cross modal scale was comparable between the three groups, indicating more circumscribed deficits in emotion recognition in MTLE compared to schizophrenia patients.

In our study, analysis of emotion scales revealed that patients with MTLE were significantly impaired compared to HC in recognizing fear and disgust, while performance on all other basic emotions did indeed lie below the performance of the two other groups (HC and extra-MTLE patients). However, these differences failed to reach significance. This

observation is in line with findings of previous studies investigating facial emotion recognition abilities in MTLE patients (Benuzzi et al., 2004; Bonora et al., 2011; Meletti et al., 2009; 2003). Furthermore, our findings are in accordance with a recent meta-analysis showing that a set of interacting fronto-temporal brain regions are active during the experiencing and perception of emotion across a range of emotion categories (Lindquist, 2011). Moreover, we did not find statistically significant correlations between epilepsy-related variables such as age at seizure onset and duration of epilepsy with CATS quotients and scales.

4.3 Theory of Mind Tests

We further investigated ToM performances in MTLE patients using other experimental paradigms that allow differentiation between different types of attribution as well as with regard to the stimulus modality they employ.

The result of the present study supports our previous finding that patients with MTLE show impairments in theory of mind abilities (Schacher et al., 2006). Extending findings of this earlier study, we could show here that these deficits are not limited to the verbal modality. Accordingly, MTLE patients were impaired in faux pas detection, made significantly worse epistemic attributions and gave fewer and less accurate interpretations of animations that elicited mentalizing compared to HC, but not compared to extra-MLTE patients (whose performance again lay between that of HC and MTLE patients). The Eyes Test was the only ToM test that failed to find significant differences between groups. While HC were highly accurate in inferring the mental states of triangles without facial expressions or other human cues, i.e., from movement cues alone, our data parallel those found in patients with autism spectrum disorders who, regardless of general intelligence, were also shown to be impaired in making mental state attributions about animated shapes (Abell et al., 2000; Castelli et al., 2002; Klin, 2000). If we directly compare the results of the MTLE patients with data from patients with autism spectrum disorder, the mean scores for intentionality attributions within ToM animations for the epilepsy patients are comparable to those of the autism groups (Castelli et al., 2002). These results suggest that MTLE patients show impairments in making mental state attributions that are comparable to individuals with autism which is characterized by impaired social functioning, communication, and interaction (Wing, 1986). Furthermore, performance on ToM animations of the Moving Triangles Task was positively correlated with emotion recognition from face and prosody, indicating that both tasks seem to measure facets

of the same construct. It is conceivable that the patients' poor understanding of others' minds is associated with impairment in verbal and auditory emotion recognition. Interestingly, as opposed to most measures of ToM, MTLE and extra-MTLE patients self-rated their empathic skills as comparable to those of HC. This fact emphasizes the importance of objective social-cognitive testing in epilepsy patients as patients may be insufficiently aware of their social-cognitive deficits.

Additionally, we explored the association between ToM performance and epilepsy-related variables and found several modest positive associations between the degree of mental state attributions with age at epilepsy onset and duration of epilepsy. From these results we can conclude that patients with earlier epilepsy onset and longer duration of epilepsy are more prone to have deficits in ToM.

4.4 Decision Making

Our results confirm previous findings (Bonatti et al., 2009; Butman et al., 2007; Delazer, Zamarian, Bonatti, Kuchukhidze et al., 2010; Delazer, Zamarian, Bonatti, Walser et al., 2010; Labudda et al., 2009) that MTLE patients have deficits in decision making under conditions of ambiguity. MTLE patients showed a significantly lower decision-making performance than HC, but not compared to extra-MTLE patients, who also obtained lower global outcome and net scores compared to HC. However, the frequency of advantageous selections markedly increased over the task for HC and extra-MTLE patients, but did not significantly increase for MTLE patients, indicating impaired learning via feedback. In addition, emotion recognition, particularly from the face and decision-making performance were correlated. A possible explanation for this association is the shared structural involvement of parts of the limbic system in decision making under ambiguity and to emotion perception (Hsu et al., 2005). Moreover, the decision-making performance was correlated with duration of epilepsy within MTLE patients.

4.5 Psychic states and traits and quality of life

In our group of clinically distinct epilepsy patients, MTLE patients did not show more psychiatric symptoms compared to extra-MTLE patients. Patients with MTLE are thought to have a particular specific risk for affective disorders because of the major involvement of the limbic system in both seizure generation in TLE and in the regulation of mood and affect. Our

study assessed psychological distress (BDI, TAS-26), personality dimensions (EPQ-RK), and quality of life (QOLIE-31) in patients with MTLE, extra-MTLE and HC.

We did not find an overrepresentation of depressive symptoms in epilepsy patients. However, as expected, both patient groups had more depressive symptoms compared to HC. Furthermore, MTLE patients reported more neurotic complaints (emotional instability, nervous tendency towards negative emotionality, and inability to cope) and were more alexithymic compared to HC. Taylor et al. (2000) examined the relationship between the alexithymia construct and emotional intelligence (represented by EQ-i scores) and found a strong negative correlation between the TAS and the EQ-i, indicating a considerable overlap of the two constructs. The higher dimensional scores for the MTLE patients on the personality dimension neuroticism corresponds with the clinical impression that patients with MTLE are often characterized by high levels of negative affect such as depression and anxiety (Bonora et al., 2011). MTLE patients rated their quality of life lower than extra-MTLE patients. This may also explain why patients with MTLE had higher neuroticism scores, because it can be assumed that psychological and social problems cause complaints of distress. The lower quality of life experienced by MTLE patients compared to extra-MTLE patients suggests that this difference is not the consequence of a chronic medical condition or AED medication per se.

4.6 Associations between social cognition and psychic states and traits, empathy, and quality of life

Furthermore, we investigated the correlations between behavioural measures of social cognition and subjective measures of psychological distress, personality dimensions, empathy and quality of life. No correlations emerged between any of these measures, indicating that social-cognitive abilities were not related to subjective measures of psychiatric symptoms, personality dimensions, self-reported empathic abilities, or quality of life. In line with these findings, Bonara et al. (2011) and Reynders et al. (2005) found that MTLE patients' ability to recognize emotions was not related to subjective measures of well-being assessed with QOLIE-31 and disease disability awareness assessed with the BDI. Interestingly, when we investigated the correlations between emotion recognition ability and subjective quality of life within the whole group of epilepsy patients, a significant correlation emerged between QOLIE Social Functioning and emotion recognition from prosody. If one considers how central emotion recognition and ToM abilities are to everyday life, one can assume that any

functional impairment due to structural and functional disconnections of the underlying neural substrates of social cognition could have a devastating impact on interpersonal relationships, social functioning and quality of life. If a person can understand semantic content but is unable to detect prosody, he or she may take a sarcastic comment quite literally. When, in addition to the missing prosodic information, changes in facial expression cannot be recognized, significant information within conversations and interactions with others may go undetected, and as a result, the individual may react inappropriately. This may create misunderstandings and disagreements with others within the private or non-private sector that can be source of social problems. It becomes clear with such examples that in order to address such issues in diagnosis and rehabilitation, the exact nature and severity of the impairment must be accurately assessed.

4.7 Side of epilepsy

In general, we found no differences between patients with seizures originating within the left versus right mesial temporal lobe with regard to their performance in emotion recognition, ToM, or decision making. Notably, the comparable performance in emotion recognition from face and prosody of both left and right MTLE patients was surprising because patients with right MTLE were expected to be more impaired (Meletti et al., 2009; 2003). However, in a recent study of this group (Bonora et al., 2011) the authors also failed to find significant differences between right- and left-sided MTLE patients in both visual and auditory emotion recognition abilities. Evidence of an effect of the side of epilepsy onset was only found for the specific emotion type fear, indicating that right-sided MTLE patients were more severely impaired. In accordance with our findings, patients with seizure onset within the right, non-language dominant hemisphere were reported to show pronounced difficulties in the recognition of fearful faces (Benuzzi et al., 2004; Hlobil, Rathore, Alexander, Sarma, & Radhakrishnan, 2008; Meletti et al., 2003).

4.8 Demographic variables and verbal intelligence quotient

Demographic variables such as gender, age, verbal intelligence, and years of education were also evaluated with regard to their possible effects on emotion recognition and theory of mind.

There was no effect of gender on any performance in the test battery. Age negatively correlated with the ability to recognize emotions from both face and prosody, to a particular degree from prosody, indicating a decline in performance with the person's age. These results are consistent with a previous finding of robust relationships between advancing age and decline in performance on prosody tasks (Kiss & Ennis, 2001). In contrast, age had no effect on ToM performance or self-reported psychological distress, personality dimensions, or empathy.

Our study replicated previous findings of significant correlations between verbal IQ and auditory emotion recognition abilities as well as a lack of correlations between verbal IQ and facial emotion recognition abilities (Bonora et al., 2011; Reynders et al., 2005). Bonora et al. (2011) ascribed the reported correlation between IQ and emotional prosody recognition to the fact that emotional prosody recognition, as opposed to facial emotion recognition, might impose more cognitive demands on the examinee. It may be assumed that prosodic stimuli require greater working memory demands than facial stimuli. This assumption is consistent with results from imaging studies that have shown the greatest activation in the right frontal regions during prosody tasks (George et al., 1996). Another significant correlation was found between verbal IQ and attributions of intentionality and the appropriateness of explanations given during ToM animations of the Moving Triangles task. Effects of education were also found on this task which is not surprising when one considers the comparatively high verbal demands. By contrast, there were no significant correlations between verbal IQ and any other ToM task. Such tasks also require attributions of intentions; however, the examinee is given more structured guidance through the answering of questions (e.g. Faux Pas Test) or receives additional input (e.g. Eyes Test). Overall, with a few exceptions, social-cognitive abilities were shown to be independent of verbal intelligence and supported numerous findings that assumed that emotion recognition and ToM are specific cognitive domains that should be delineated from general intelligence (Baron-Cohen et al., 1997; Karmiloff-Smith, Klima, Bellugi, Grant, & Baron-Cohen, 1995). Although only patients who had mild to moderate impairments in the domains of attention, executive function, and episodic memory were included in this study, we cannot completely rule out effects of cognitive deficits, especially in executive functions, on emotional processing and ToM.

5. Conclusions

Our study demonstrated that patients with MTLE are at risk of impairments in various aspects of social cognition. Patients with epilepsies not originating from the medial temporal lobes may also be at risk, albeit to a much lesser extent. Therefore, the specific type of epilepsy, particularly MTLE, and not epilepsy per se as a chronic disorder or its treatment with AED can be considered as significant risk factor in developing social-cognitive deficits. It is reasonable to argue that the frequent presence of deficits in social cognition in MTLE patients contributed to the formulation of the concept of an “interictal personality syndrome” or a “Waxman-Geschwind Syndrome”. Further neurobehavioural research in this field is necessary to reveal the causes and demystify the concept of the “epileptic personality” and hopefully provide new approaches for treatment.

Acknowledgments

This work was supported by the Swiss Epilepsy Foundation.

We thank Prof. Dr. Eugen Trinka, Prof. Dr. Gerhard Luef and Dr. Iris Unterberger for enabling us to recruit patients from the Epilepsy Unit of the Department of Neurology, Innsbruck Medical University.

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Supplementary Table S1 Clinical data from MTLE and extra-MTLE patients.

Patient	Type of Epilepsy	Sex	Handedness	Age	Mean Age at Epilepsy Onset in Years	Duration of Epilepsy in Years	Side of Seizure Onset	MRI Findings
A1	MTLE	w	RH	58	27	31	Right	HS
A3	MTLE	w	RH	27	3	24	Right	HS
A3	MTLE	w	RH	21	1	20	Right	HS
A4	MTLE	m	RH	26	23	3	Right	HS
A5	MTLE	w	RH	27	6	21	Right	HS
A6	MTLE	m	RH	53	23	30	Right	HS
A7	MTLE	m	RH	45	36	9	Right	HS
A8	MTLE	m	RH	53	3	50	Right	HS
A9	MTLE	w	RH	42	30	12	Right	HS
A10	MTLE	w	RH	32	31	1	Right	HS
A11	MTLE	m	RH	47	32	15	Right	HS
A12	MTLE	w	RH	30	29	1	Left	Space-consuming cystic lesion in the parahippocampal gyrus
A13	MTLE	m	RH	65	35	30	Left	HS
A14	MTLE	w	RH	42	34	8	Left	HS

Patient	Type of Epilepsy	Sex	Handedness	Age	Mean Age at Epilepsy Onset in Years	Duration of Epilepsy in Years	Side of Seizure Onset	MRI Findings
A15	MTLE	w	RH	26	23	3	Left	Dysplasia of amygdala
A16	MTLE	w	RH	26	23	3	Left	Dysplasia of amygdala
A17	MTLE	m	RH	18	17	1	Left	HS
A18	MTLE	w	RH	44	9	35	Left	HS
A19	MTLE	w	RH	46	37	9	Left	HS
A20	MTLE	w	RH	20	4	16	Left	HS
A21	MTLE	w	RH	15	10	5	Left	HS
A22	MTLE	m	RH	33	18	15	Left	HS
A23	MTLE	w	RH	35	22	13	Left	HS
A24	MTLE	m	RH	19	17	3	Left	Space-consuming lesion in the fusiform gyrus
A25	MTLE	m	RH	33	17	16	Left	HS
A26	MTLE	m	RH	34	33	1	Left	Dysplasia of amygdala
A27	MTLE	m	RH	30	10	20	Left	HS
A28	MTLE	w	RH	17	13	4	Left	HS

Patient	Type of Epilepsy	Sex	Handedness	Age	Mean Age at Epilepsy Onset in Years	Duration of Epilepsy in Years	Side of Seizure Onset	MRI Findings
B1	SGE*	m	RH	24	14	10	Right	Space-consuming cystic lesion parieto-occipital
B2	SGE	m	RH	45	38	7	Left	Tumour in the paracentral lobule
B3	IGE*	m	RH	29	18	11		
B4	IGE	w	RH	18	13	5		
B5	IGE	w	RH	25	20	5		
B6	IGE	m	RH	39	10	29		
B7	IGE	m	RH	45	40	5		
B8	IGE	m	RH	60	20	40		
B9	IGE	w	RH	43	11	32		
B10	IGE	m	RH	33	19	14		
B11	IGE	w	RH	21	4	17		
B12	CGE*	m	RH	23	18	5		
B13	CGE	m	RH	32	25	7		
B14	CGE	m	RH	30	10	20		

*SGE=Symptomatic Generalized Epilepsy; *IGE=Idiopathic Generalized Epilepsy; *CGE=Cryptogenic Generalized Epilepsy

Supplementary Table S2 The results for each group on the self-report questionnaires of psychological distress (BDI, TAS-26), personality dimensions (EPQ-RK), empathy (SPF) and quality of life (QUOLIE-31).

Variable	Healthy Controls Mean (SD)	Extra-MTLE Patients Mean (SD)	MTLE Patients Mean (SD)	MANOVA (and *post hoc* Bonferroni) or or Independent Samples *t*-Test or Kruskal Wallis (and pairwise Mann Whitney) *F*	*p*	Bonferroni	Effect Size
Toronto Alexithymia Scale Overall Scale	37.29 (7.84)	39.65 (8.83)	45.54 (11.05)	$F(2, 67) = 4.68$	.01**	HC < **MTLE	0.13
Toronto Alexithymia Scale Difficulty Identifying Emotions	11.78 (3.05)	14.15 (5.33)	17.07 (6.24)	$F(2, 67) = 6.73$	.002*	HC < ***MTLE	0.18
Toronto Alexithymia Scale Difficulty Communicating Emotions	11.61 (3.73)	12.43 (4.26)	13.96 (3.79)	$F(2, 67) = 2.73$	.07		0.08

Toronto Alexithymia Scale							
Externally Oriented Thinking	13.85 (3.11)	13.16 (4.29)	14.53 (4.17)	$F(2, 67) = 0.58$	.5		0.02
Beck Depression Inventory						HC < ***MTLE,	
Overall Score	1.31 (2.46)	6.77 (8.39)	10.43 (9.19)	$x^2 = 27.78$	.001**	**extra-MTLE	
Eysenck Personality Questionnaire							
Neuroticism	3.61 (2.71)	3.75 (3.08)	5.75 (2.95)	$F(2,65) = 4.02$	.02*	HC < **MTLE	0.12
Eysenck Personality Questionnaire							
Psychoticism	7.11 (3.40)	7.71 (3.07)	6.75 (3.62)	$F(2, 65) = 2.36$	.1		0.07
Eysenck Personality Questionnaire							
Extraversion	6.89 (2.78)	7.42 (2.23)	7.39 (2.32)	$F(2, 66) = 0.80$	.45		0.03
Eysenck Personality Questionnaire Lie							
Scale	6.54 (3.57)	8.33 (1.50)	6.64 (2.23)	$F(2, 66) = 2.06$	.14		0.06
Saarbruecken Personality Questionnaire							
Fantasy	14.38 (2.46)	12.38 (3.80)	13.33 (2.88)	$F(2, 66) = 1.74$	.19		0.05
Saarbruecken Personality Questionnaire							
Empathic Concern	15.10 (2.26)	15.54 (3.50)	15.11 (1.78)	$F(2, 66) = 0.17$	.84		0.01
Saarbruecken Personality Questionnaire							
Perspective Taking	14.59 (2.81)	14.31 (4.23)	14.26 (2.58)	$F(2, 66) = 0.14$	.87		0.01
Saarbruecken Personality Questionnaire							
Personal Distress	10.93 (3.21)	10.54 (4.27)	11.41 (3.63)	$F(2, 66) = 0.19$	.83		0.01

Quality of Life in Epilepsy-31 Overall Score	72.13 (12.80)	56.01 (15.65)	$t(1, 40) = -3.33$	.002**	MTLE < **Extra-MTLE
Quality of Life in Epilepsy-31 Overall QOL	74.82 (15.39)	58.73 (18.55)	$t(1, 40) = -2.80$	.008**	MTLE < **Extra-MTLE
Quality of Life in Epilepsy-31 Emotional Well Being	68.57 (19.40)	58.61 (16.68)	$t(1, 40) = -1.73$	.09	
Quality of Life in Epilepsy-31 Social Functioning	82.86 (13.85)	59.68 (22.04)	$t(1, 40) = -3.58$	.001**	MTLE < **Extra-MTLE

* MANOVA (and *post hoc* Bonferroni) or Independent Samples *t*-Test is significant at the $p<.05$ level (two-tailed).

** MANOVA (and *post hoc* Bonferroni) or Independent Samples *t*-Test is significant at the $p<.01$ level (two-tailed).

*** Kruskal Wallis (and pairwise Mann Whitney) is significant at the $p<.001$ level (two-tailed).

Sample sizes vary slightly by subgroup due to missing values.

Supplementary Table S3 Pearson's product-moment correlations between Emotion Recognition measures (CATS Quotients), Theory of Mind measures (Eyes Test, Moving Triangles, Faux Pas Test), and the Decision-Making Task (Iowa Gambling Task).

n=66 [a]	CATS, ARQ	CATS, PRQ	CATS, ERQ	Eyes Test	MT, ToM, I.	MT, ToM, A.	MT, ToM, L.	Faux Pas Test	IGT
CATS Affect Recognition Quotient (ARQ)	1								
CATS Prosody Recognition Quotient (PRQ)	.49**	1							
CATS Emotion Recognition Quotient (ERQ)	.84**	.83**	1						
Eyes Test Total Score	.16	.05	.12	1					
Moving Triangles, ToM Intentionality (I)	.34**	.45**	.50**	.12	1				
Moving Triangles, ToM Appropriateness (A)	.19	.43**	.36**	.02	.70**	1			
Moving Triangles, ToM Length (L)	.21	.15	.24	.13	.57**	.52**	1		

Faux Pas Test									
Total Score	.01	.23	.15	.25*	.22	.06	.18	1	
Iowa Gambling Task (IGT)									
Global Outcome Score	.43**	.29*	.41**	.15	.25	.13	.20	.20	1

* Correlation is significant at the $p<.05$ level (two-tailed).

** Correlation is significant at the $p<.01$ level (two-tailed).

[a]CATS $n=66$, Eyes Test $n=71$, Moving Triangles $n=63$, Faux Pas Test $n=69$, Iowa Gambling Task $n=53$

Sample sizes vary slightly by subgroup due to missing values.

5.2 Advanced social cognition and amygdalar fMRI response in patients with unilateral mesial temporal lobe epilepsy

Sarah D. Broicher, Franziska Arter, Thomas Grunwald, Dominik Huber, Martin Kurthen, Günter Krämer, Hennric Jokeit

Swiss Epilepsy Centre, Zürich, Switzerland

Corresponding author:
Sarah Dinah Broicher, MSc
Swiss Epilepsy Center
Bleulerstrasse 60, 8008 Zürich, Switzerland
Tel.: ++41/44/387-6348
Fax: ++41/44/387-6134
e-mail: Sarah.Broicher@swissepi.ch

Key words: amygdala, fMRI, social cognition, temporal lobe epilepsy, theory of mind
Number of text pages: 14
Word count: 4 572
Number and proposed size of figures: 3; 147 KB
Number and proposed size of tables: 1; 88 KB

SUMMARY

Purpose: Patients with mesial temporal lobe epilepsy (MTLE) frequently show ipsilateral amygdalar dysfunctions as well as deficits in "Theory of Mind" (ToM) tasks. However, the role of the amygdala in higher-order social cognition such as ToM is still a matter of debate. Here we investigated whether the asymmetry ratio of functional magnetic resonance imaging (fMRI) of amygdalar activity is related to performance in an advanced ToM task, the recognition of faux pas test.

Methods: We investigated 29 adult patients, aged 18-60 years (fourteen males), with refractory unilateral MTLE (16 left-sided, 13 right-sided) using fMRI and neuropsychological testing. The ToM task used was a shortened version of the recognition of faux pas test which comprises three selected stories. No patient had structural abnormalities other than within the left or right mesial temporal lobe. Brief video sequences showing animated fearful faces contrasted by landscapes were presented to the subjects during standard fMRI acquisition.

Key findings: In the faux pas test, right-sided MTLE patients performed worse (p=.02) compared to left-sided MTLE patients. Amygdala activation was reduced ipsilateral to the side of seizure onset in the majority of patients (p<.001). Patients with right- (r= -.40; p=.04, one-tailed) but not left-sided MTLE (left-sided MTLE: r=-.05, p=.41, one-tailed) presented a significant correlation between amygdalar signal asymmetry and faux pas test performance. Patients with right-sided MTLE and more ipsilateral amygdalar activity performed better than those with reduced ipsilateral activity. Stepwise multiple regression analysis revealed that the amygdalar asymmetry ratio did not significantly contribute to the explanation of faux pas test performance variability beyond that explained by side of MTLE.

Significance: We confirmed previous results that right-sided MTLE is associated with impaired performance in an advanced theory of mind task and that fMRI reactivity of the amygdalae lateralizes MTLE well. In patients with right-sided MTLE, ipsilateral amygdalar reactivity is related to ToM test performance. Right-sided MTLE, not unilateral amygdala dysfunction per se, can be considered a risk factor for deficits in higher-order social cognition. Our findings support the hypothesis of a hemispheric lateralization for higher-order ToM performances.

INTRODUCTION

Mesial temporal lobe epilepsy (MTLE) is typically associated with lesions involving temporal limbic structures such as the hippocampus and amygdala. The role of the hippocampus and adjacent cortical regions in memory functions is well established and is taken into account in the diagnostic workup in candidates for epilepsy surgery. In contrast, the role the amygdala plays in clinical and neuropsychological symptoms and in the context of epilepsy surgery is less well understood.

Recently, we showed that ipsilateral amygdala reactivity in fMRI is reduced in response to fearful faces in the majority of patients with unilateral MTLE (Schacher, Haemmerle et al., 2006). Moreover, we found that MTLE patients, as compared to patients with epilepsy not originating within the MTL and healthy controls, were impaired in their ability to recognise social faux pas (Schacher, Winkler et al., 2006). The faux pas test can be seen as a "higher-order" or "advanced" theory of mind (ToM) task as it goes beyond simple attributions and requires inferences regarding others' mental states with respect to their thoughts and beliefs ("cognitive ToM component") as well as with respect to their emotional states and feelings ("affective ToM component") (Shamay-Tsoory & Aharon-Peretz, 2007; Stone et al., 2003; Stone et al., 1998). Particularly patients with right-sided MTLE performed worse on this test than patients with left-sided MTLE.

In epilepsy, the laterality of the seizure focus has especially been considered as a potential risk factor for disturbances in basal aspects of social cognition such as the processing of emotional stimuli. TLE-patients, in particular patients with early seizure onset and right or bilateral medial temporal dysfunction, were found to have pronounced difficulties in the recognition of fearful faces (Benuzzi et al., 2004; Bonora et al., 2011; Meletti et al., 2009; 2003). Lesion studies have also found impairments in the recognition of fear after right, rather than left, amygdala damage (Adolphs et al., 2001; Anderson, Spencer, Fulbright, & Phelps, 2000). However, since little research has been conducted on higher-order social cognition in MTLE, evidence on the question of whether patients with right-sided MTLE were at increased risk for disturbances of higher-order social cognition is still lacking.

ToM tasks are thought to activate a consistent set of frontal and temporal brain regions (Amodio & Frith, 2006; Stone et al., 1998). In their current overview of functional imaging studies investigating the neural basis of ToM, Carrington and Bailey (Carrington & Bailey, 2009) found the amygdala to be less consistently activated. However, there is converging evidence that the amygdala, besides its central role in the perception and processing of

socially relevant information (Adolphs, 2003; Spezio et al., 2007), is at the core of the ability to interpret the mental states of others (Baron-Cohen et al., 2000; Castelli et al., 2000; Gallagher & Frith, 2004; Stone et al., 2003).

Disagreement remains as to what degree the amygdala merely supports the development of ToM abilities (Frith & Frith, 2003; Shaw et al., 2004; Tager-Flusberg & Sullivan, 2000) or whether it represents an essential part of the ToM network (Channon & Crawford, 2000; Happe et al., 1999; Sommer et al., 2008; Stone et al., 2003). The majority of authors agree with the latter supposition, which receives support in particular from lesion studies that indicate a clear connection between uni- and bilateral lesions of the amygdala and deficits in ToM (Heberlein & Adolphs, 2004a; Stone et al., 2003). A recent meta-analytic review of the literature on human neuroimaging of emotion showed that a set of interacting fronto-temporal brain regions, including the amygdala, are active during the experiencing and perception of emotion across a range of emotion categories (Lindquist, 2011). The amygdala was found to be more active during fear perception, but also during all other emotion categories. Whereas a considerable number of studies support the close relationship between emotion recognition and ToM using behavioural data (Bora et al., 2005; Brune, 2005a; Buitelaar & van der Wees, 1997; Dyck, Piek, Hay, Smith, & Hallmayer, 2006; Henry, Phillips, Crawford, Ietswaart, & Summers, 2006), but see also (Langdon, Coltheart, & Ward, 2006; Phillips, MacLean, & Allen, 2002 for divergent results), the only study reported to date which has investigated its relationship on both behavioural and neuronal levels was a recent event-related fMRI study by Mier et al. (2010). The authors reported a positive correlation between the number of correctly recognized emotions and correctly recognized intentions as well as overlapping patterns of activation during performance of both tasks. Areas conjointly activated by both tasks included, among others, the amygdala.

The purpose here is to evaluate whether functional impairments of the amygdalae as established by fMRI are associated with degraded performance in a recognition of faux pas test in patients with MTLE. Our hypothesis was that amygdala activity induced by fearful face processing is associated with performances in higher-order ToM tasks.

Following the finding of our previous investigation (Schacher, Winkler et al., 2006) which suggested that the right hemisphere could be more strongly associated with theory of mind abilities in epilepsy patients, we further wanted to assess the relationship between ToM abilities and the laterality of the epileptogenic zone and amygdala BOLD reactivity within the same group of patients.

PATIENTS AND METHODS

Subjects

Thirty-one patients aged 18 to 60 (mean 35.97 years, SD 13.09; 14 men, 17 women; 29 right handed, 1 left handed and 1 ambidexter) with medically refractory focal epilepsies (mean age at seizure onset 13.32 years, SD 10.65 and epilepsy duration 22.32 years, SD 14.83) were investigated (see Table 1). Patients were recruited from consecutive inpatient admissions to the Swiss Epilepsy Center between 2006 and 2010.

Patients underwent neurological examination and routine EEG recordings using the 10-20 system. Seizure types and epilepsy syndromes were diagnosed according to the classification of the International League Against Epilepsy (1989; 1981).

All patients had MTLE with a clear unilateral seizure onset of MTL origin, as shown by continuous interictal and ictal video/EEG monitoring with scalp and sphenoidal electrodes and a clear diagnosis of MTL pathology, as shown by high-resolution routine MRI. Of the thirty-one patients, thirty had hippocampal sclerosis (HS) (twelve right- and eighteen left-sided). The MRI of one patient revealed a space-consuming lesion of unclear pathology at the medial border of the amygdala (Table 1). All patients were treated with first line antiepileptic drugs (AEDs).

Language laterality was determined either by use of an fMRI paradigm employing a verbal fluency task (n=29) or by Wada test if the fMRI was inconclusive (n=2) (Woermann et al., 2003). The majority of patients (29/31) had left-sided language dominance; two had bilateral language representations in fMRI. Handedness was determined by the Edinburgh Handedness Inventory (Table 1).

Table 1

Demographic, epilepsy, MRI, fMRI and handedness data of 31 patients with mesial temporal lobe epilepsy.

Patients	Sex	Age	Age at seizure onset, y	Duration of epilepsy, y	Side of seizure onset	Morphologic lesion	Amygdala activation	LI	Handedness (right/left)
1	m	18	6	12	Left	HS	Right>Left	-0.98	RH
2	w	18	1	17	Left	HS	Right>Left	-0.54	LH
3	w	39	38	1	Left	HS	NA		RH
4	m	26	1	25	Left	HS	Unilat. right	-1	RH
5	m	44	15	29	Left	HS	Unilat. right	-1	RH
6	w	28	15	13	Left	HS	Unilat. right	-1	RH
7	w	42	19	23	Left	HS	Left>Right	0.93	RH
8	w	55	9	46	Left	HS	NA		RH
9	w	23	7	16	Left	HS	Unilat. right	-1	RH
10	w	45	9	36	Left	HS	Right>Left	-0.64	RH
11	w	31	1	30	Left	HS	Right>Left	-0.92	RH
12	w	40	11	29	Left	HS	Right>Left	-0.55	RH
13	m	19	18	1	Left	HS	Bilateral	-0.15	RH
14	w	49	5	44	Left	HS	Unilat. Right	-1	RH
15	m	33	17	16	Left	HS	Right>Left	-0.75	RH
16	m	33	18	15	Left	HS	Bilateral	-0.21	RH
17	m	20	11	9	Left	HS	Left>Right	0.38	RH
18	w	18	12	6	Left	HS	Left>Right	0.82	RH
19	w	46	14	32	Right	HS	Unilat. left	1	RH
20	w	18	7	11	Right	HS	Bilateral	0.25	RH
21	w	45	3	42	Right	HS	Unilat. left	1	RH
22	m	53	2	51	Right	HS	Right>Left	-0.51	Ambidexter
23	m	46	7	39	Right	HS	Unilat. left	1	RH
24	w	24	1	23	Right	HS	Unilat. left	1	RH
25	m	45	14	31	Right	HS	Left>Right	0.98	RH
26	m	47	10	37	Right	HS	Left>Right	0.4	RH
27	m	26	23	3	Right	HS	Unilat. left	1	RH
28	m	21	18	3	Right	HS	Unilat. left	1	RH
29	m	46	29	17	Right	HS	Unilat. left	1	RH
30	w	60	45	15	Right	Unclear pathology at the medial border of the amygdala	Unilat. left	1	RH
31	w	57	27	30	Right	HS	Bilateral	-0.1	RH

Abbreviations: m – man, w – woman, y – years, HS – hippocampal sclerosis, unilat. – unilateral, LI – lateralization index, RH – right-handed, LH – left-handed, NA – not applicable.

Mentally handicapped patients were excluded (IQ<70). All patients had an IQ equal to or greater than 75. Further exclusion criteria were psychiatric disorders, whereby adjustment disorders and mild to moderate depression constituted an exception to this rule since it was assumed that they are comorbid symptoms of temporal lobe epilepsy (Glosser et al., 2000; B. Hermann et al., 2008). Adjustment disorders and depressive mood were diagnosed by a highly experienced clinical psychologist using ICD-10 criteria.

Amygdala activation was measured in all patients with a fearful face paradigm (Schacher, Haemmerle et al., 2006). In addition to the fearful face paradigm, subjects underwent neuropsychological investigation and performed a typical advanced ToM task in which they had to detect a faux pas in a brief prose passage (Stone et al., 2003). fMRI and neuropsychological testing took place either on the same (n=19) or different days (n=12), but did not take place more than three months apart, except in one patient in whom this interval was seven months.

All patients gave written informed consent following a thorough explanation of the study. The present study was performed in adherence of the Declaration of Helsinki and was also approved by the local medical ethics committee.

Recognition of faux pas test

All 31 subjects performed a shortened version of a faux pas test (Stone et al., 2003) that comprised three selected stories. The shortened version of the faux pas test was previously investigated in healthy controls and patients with TLE by Schacher et al. (Schacher, Winkler et al., 2006). Further information related to the selection procedure of the stories has been described by Schacher et al. (2006). The faux pas test is a ToM test for adults and estimates the ability to recognize and understand a social faux pas.

A faux-pas is understood as a statement in which the speaker unintentionally offends or insults another person. For example, person “A” complains to person “B” about a wedding present without realising that he is talking to the person from whom he received it. The faux pas test measures several ToM components by including deductions concerning epistemic mental states as well as affective mental states (Schacher, Winkler et al., 2006; Stone et al., 2003; 1998). Patients were asked to read each story silently, knowing that they would then be asked questions about the story. There were three questions regarding interpersonal relations and emotional states, and the last one was a control question to control for text comprehension (see Appendix). The first question concerned the detection and comprehension of the faux pas, while question two and three required the patient to impute the mental state of

andattribute emotions to another. The data analysis involved the sum of correct answers to the first three questions, where each question was scored with one point, resulting in maximum nine points for all three stories. Points for the control question were excluded from the total score but served as an indicator of text comprehension.

Additionally, to control for language comprehension, data from the Chapman-Cook test were used (Chapman, 1923). This test comprises 12 short text passages in which a single word does not fit with the overall context of the text. All patients included in the study had intact language-comprehension abilities (i.e., all answered every faux pas control question correctly and correctly identified at least 11 of the 12 words in the Chapman Cook test).

Intelligence quotients (IQs) were estimated using the full-scale IQ derived from the German version of the Wechsler Adult Intelligence Scale, Revised (HAWIE-R) (Tewes, 1994) and a vocabulary-based intelligence test (MWT-B). In this test, patients were required to identify a real word from a choice of four pseudo-words with increasing test difficulty (Lehrl et al., 1995). The mean score for Full-Scale, Verbal, and Performance IQ was within the normal range (Full-Scale IQ: M=98.48; SD=14.10; Verbal IQ: M=94.93; SD=15.18; Performance IQ: M=103.17; SD=16.65). The majority of patients (80.65%; 25 out of 31) tested had a Full-Scale, Verbal and Performance IQ within the norm range (i.e., above 85).

fMRI task design

The fMRI paradigm used here has been extensively described by Schacher et al. (2006). The applied block design paradigm consisted of eight activation and eight baseline blocks each lasting 24 seconds. The activation condition comprised 75 brief episodes (two to three seconds) from thriller and horror films. All episodes showed close-ups of the faces of actors who were expressing fear with high intensity. None of the episodes showed violence or aggression. During baseline blocks 72 short episodes of similar length with dynamic landscape video recordings were presented. Video clips of dull domestic landscapes were used owing to their stable low emotional content while their general visual stimulus properties were comparable with the movie clips. Frequency and duration of the sequences were matched in the activation and control conditions. Stimuli were presented via a back-projection screen and viewed through a tilted overhead mirror. Prior to beginning subjects were told that they would see rapid presentations of film sequences depicting fearful faces intermixed with landscape film sequences. They were instructed to relax while watching the film and to focus on the eyes of the actors during the activation blocks.

MRI acquisition

fMRI data were recorded using a 1.5 T system (Magneton Sonata, Siemens, Erlangen, Germany) and a 3.0 T system (Achieva Philips Medical Systems, Best, The Netherlands). A comparison between data which were collected on different systems with different MRI-parameters is likely unproblematic as images were considered and evaluated intra-individually and only the activity ratios of different patients were compared. Routine skull base magnetic resonance imaging (MRI) protocols were performed for each patient. MRI sequences included T1-weighted spin echo and gradient echo three-dimensional multiplanar reconstruction images (MPRAGE), coronal T2-weighted turbo spin echo, T2-weighted fast fluid attenuated inversion recovery (FLAIR) and diffusion weighted sequences. Coronal T2-weighted and FLAIR slices were 1-3 mm thick and were acquired at 90° perpendicular to the long axis of the hippocampi. Subjects were sited in the head coil with ear pads and foam padding to minimize head motion and noise exposition. T1-weighted (T1W) acquisition parameters, according to the pre-existing protocols, were 176 axial slices with 1-mm single-slice thickness, repetition time (TR) 8.2 ms, echo time (TE) 3.93 ms, 8° flip angle, field of view (FOV) 250 mm, and 288 x 288 matrix on the 3.0 T system, and TR 1.900 ms, TE 3.93 ms, 15° flip angle, FOV 250 mm, and 256 x 256 matrix on the 1.5 T system.

Functional data were acquired using echo planar imaging (EPI) T2*-weighted sequence. The following parameters were applied to measure amygdalar activation: 18 coronal slices on the 3.0 T vs. 12 coronal slices on the 1.5 T, 4-mm slice thickness and 0-mm interslice gap vs. 5-mm slice thickness and 1-mm interslice gap, TR 1500 ms vs. TR 1490 ms, TE 35 ms vs. TE 60, 75° flip angle vs. 90° flip angle, FOV 220 mm vs. FOV 250 mm, matrix size 64 x 64, voxel size 2.75 x 2.75 x 4 mm vs. voxel size 3.9 x 3.9 x 5 mm, reconstructed into an image matrix of 128 x 128 on both systems. Coronal slices were geared orthogonally to the hippocampal formation and were spread over the anterior temporal lobe.

Data analyses

Functional MRI single subject data analysis was performed with BrainVoyager QX software (BrainInnovation, Maastricht, the Netherlands). In the primary analyses the data were preprocessed with (1) three-dimensional motion correction and (2) trend removal by temporal fast Fourier transform-based high-pass filtering and transformed into Talairach co-ordinate space. Images of the fearful face task were additionally spatially smoothed with a full width at half-maximum of 4 mm.

For multiple regression analysis a general linear model (GLM) with the predictor for the activation condition was computed. The time courses of the predictor were obtained by using a linear model of the hemodynamic response. The overall model fit was assessed using F statistics. Significant differences between the experimental conditions were assessed using contrast (*t*) maps.

For images in the fearful face task, individual volumes of interests (VOIs) were defined for the amygdalar region. VOIs were specified functionally for each patient separately using a predefined statistical threshold of $p<.001$ (see Table 1). Anatomic borders of the functional clusters were the uncal recess caudally and the optical chiasm rostrally and white matter superiorly. For each VOI the number of activated voxels was counted in the left and right hemisphere on a predefined threshold of $p<.001$. Asymmetry ratios (AR) were defined for the number of significantly activated voxels in the amygdalar/periamygdalar area using the formula: AR = (left - right)/(left + right). If the AR was greater than 0.25 and less than -0.25 these cases were categorized as asymmetric.

Statistical Analysis

Statistical evaluations were performed with the SPSS 15 software package (SPSS Inc, Chicago, IL, U.S.A).

We applied the non-parametric Mann-Whitney U test to examine whether right- vs. left-sided MTLE patients and men vs. women differed in their overall score in the faux pas test.

We additionally used nonparametric correlation analysis (Kendall Rank Correlation Coefficient) to investigate the relation between age at seizure onset, duration of epilepsy, age, Full-Scale, Verbal and Performance IQ, and the ability to detect faux pas.

Since data are not measured on an interval scale and deviate from a normal distribution, we computed the Kendall Rank Correlation Coefficient of the “performance in the faux pas test” and “Asymmetry Ratio (AR)”. Because of the directional hypothesis of a better performance in the faux pas test and increased activation of the right amygdala in right-sided MTLE patients, single correlations between fMRI asymmetry ratio and performance in the faux pas test for subgroups of MTLE patients were carried out at a significance level set at $p<.05$ (one-tailed).

A stepwise multiple regression analysis was performed to examine the possible predicting abilities of side of MTLE and AR for faux pas test performance. The level of significance was set to $p=.05$ (two-tailed tests).

RESULTS

Recognition of faux pas test

Since the following analyses refer exclusively to the performance in the faux pas test, the whole sample (*n*=31) was included.

None of the evaluated patients reached the maximum score of nine points in the faux pas test (Median=6.50). The majority of patients (87.1%; 27 of 31) reached an aggregate value lying under the cut-off of 7.75 points, the 25th percentile based on normative data of 50 healthy control subjects (unpublished data).

Patients with right- (*n*=13) and left-sided (*n*=18) MTLE differed (Mann-Whitney U test: U=57.00, *p*=.02, two-tailed; Fig. 1) with regard to their overall scores in the faux pas test.

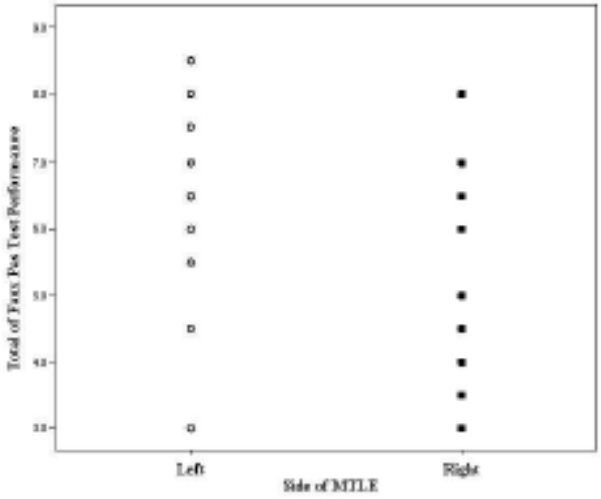

Figure 1 Faux pas test performance in left- and right-sided mesial temporal lobe epilepsy (MTLE) patients. White dot=left-sided MTLE (n=16); black square=right-sided MTLE (n=13). *Mann-Whitney* U *test* (*p*=.02). Note that due to overlapping data points the actual number of dots and squares do not represent the total number of patients.

Patients with right-sided MTLE (Mean Rank=11.38) performed significantly worse than patients with left-sided MTLE (Mean Rank=19.33). There was neither a significant difference between men (*n*=14; Mean Rank=15.14) vs. women (*n*=17; Mean Rank=16.71) (Mann-Whitney U test: U=107.00, *p*=.63, two-tailed) nor between patients with mild to moderate depression (*n*=5; Mean Rank=16.10) vs. patients without any depressive symptoms (*n*=26; Mean Rank=15.98) (Mann-Whitney U test: U=64.50, *p*=.98, two-tailed).

Subgroups of right-sided vs. left-sided MTLE patients did not differ with regard to age (Mann-Whitney U test: U=73.50, *p*=.09, two-tailed), age at epilepsy onset (Mann-Whitney U test: U=101.50, *p*=.53, two-tailed), duration of epilepsy (Mann-Whitney U test: U=95.00,

p=.40, two-tailed), and Full-Scale, Verbal and Performance IQ (Mann-Whitney U test; Full-Scale IQ: U=96.00, *p*=.40, two-tailed; Verbal IQ: U=93.50, *p*=.65, two-tailed; Performance IQ: U=90.50, *p*=.55, two-tailed).

Non-parametric correlational analysis revealed a negative association between the MTLE patient's age and deficits in faux pas test performance (Kendall *r*=-.32; *p*=.02, two-tailed). Age at seizure onset (Kendall *r*=-.06; *p*=.67, two-tailed), duration of epilepsy (Kendall *r*=-.23; *p*=.08, two-tailed) and Full-Scale, Verbal and Performance IQ (Kendall; Full-Scale IQ: *r*=.12; *p*=.36, two-tailed; Verbal IQ: *r*=.11; *p*=.43, two-tailed; Performance IQ: *r*=.15; *p*=.27, two-tailed) were not related to faux pas test performance.

fMRI asymmetry ratio (AR)

T2*-weighted contrast differences were found within the amygdalae in all but two subjects in response to watching video sequences with fearful faces compared to watching landscape scenes (*p*<.01). Due to the nonquantifiable AR of two patients, they were excluded from further analysis. In the following we refer to the sample excluding these two patients (*n*=29). The activation focus was located in the superior portion of the amygdala, as found by Schacher et al. (Schacher, Haemmerle et al., 2006). The mean AR of the amygdala was .05 (SD=.83).

In patients with right-sided MTLE (*n*=13) the mean of the AR was .69 (SD=.52), which reflects predominant contralateral left-sided activation of the amygdala. Patients with left-sided MTLE (*n*=16) showed the opposite activity pattern with predominant contralateral right-sided amygdala activation (AR=-.47, SD=.66). The AR of patients with right-sided MTLE significantly differed from patients with left-sided MTLE (Mann-Whitney U test: U=13.00, *p*<.001; Fig. 2).

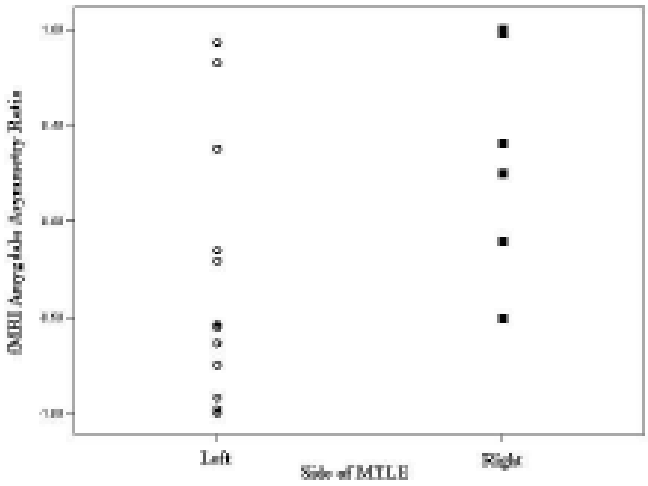

Figure 2 Asymmetry ratio of fMRI amygdalar activity in left- and right-sided mesial temporal lobe epilepsy (MTLE) patients. White dot=left-sided MTLE (n=16); black square=right-sided MTLE (n=13). *Mann-Whitney* U *test* (p<.001). Note that due to overlapping data points the actual number of dots and squares do not represent the total number of patients.

In patient seven, 17 and 18 with left-sided MTLE and patient 22 with right-sided MTLE we found an asymmetric activation of the amygdala ipsilateral to the seizure onset side.

Of the 29 patients, bilateral amygdalae activation without appreciable asymmetry was observed in four patients (patients 13, 16, 20 and 31), unilateral right-sided activation in five, unilateral left-sided activation in eight, lateralized right-sided activation in seven and lateralized left-sided activation in five. Altogether, 11 out of 13 patients with right-sided MTLE showed a positive AR and 13 out of 16 patients with left-sided MTLE showed a negative AR.

In relation to the side of seizure onset, amygdala activation was contralateral in 21 out of 29 (72 %) patients, and ipsilateral in four (14%) patients. In two patients with left-sided MTLE as well as two patients with right-sided MTLE, amygdala activation was bilateral (14%).

Correlation between fMRI asymmetry ratio and performance in the faux pas test

The bivariate non-parametric correlation coefficient between the AR and the total score in the faux pas test was r=-.31, p=.03, two-tailed (n=29) (Fig. 3). Patients with predominantly right-sided amygdalar signal tended to perform better in the faux pas test.

Post hoc, a better performance in the faux pas test with increased activation of the right amygdala was found within the subgroup of right-sided MTLE patients (r=-.40; p=.04, one-tailed), while this was not the case in the subgroup of left-sided MTLE patients (left-sided MTLE: r=-.05, p=.41, one-tailed; Fig. 3).

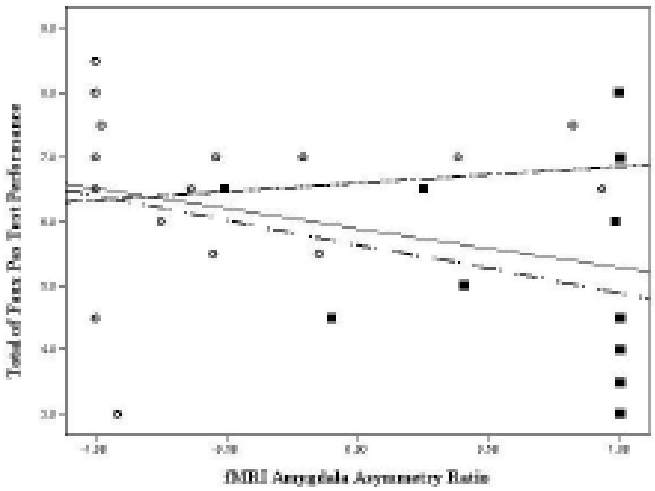

Figure 3 Correlations between the total score in the faux pas test and the asymmetry ratio of fMRI amygdalar activity in mesial temporal lobe epilepsy (MTLE). White dot=left-sided MTLE (n=16); black square=right-sided MTLE (n=13); solid line=correlation for left- and right-sided MTLE patients (r=-.31, p=.03, two-tailed); line with three dots=correlation for left-sided MTLE patients (r=-.05, p=.41, one-tailed); line with one dot=correlation for right-sided MTLE patients (r= -.40; p=.04, one-tailed). Note that due to overlapping data points the actual number of dots and squares do not represent the total number of patients.

Intercorrelation between fMRI asymmetry ratio, side of MTLE and performance in the faux pas test

A stepwise multiple regression analysis was conducted using performance in the faux pas test as a dependent variable and the side of MTLE and the fMRI asymmetry ratio as the predictor variables. The results of the stepwise analysis revealed that the side of MTLE, not the AR, was a significant predictor (r=.43; F=6.30, p=.02, two-tailed) of faux pas task performance.

DISCUSSION

We reproduced data from two previous independent former studies (Schacher, Haemmerle et al., 2006; Schacher, Winkler et al., 2006) using a single sample of 29 consecutive pharmacoresistant MTLE patients.

Patients with MTLE were tested using a shortened version of the faux pas test in which patients with MTLE were previously shown to be specifically impaired (Schacher, Winkler et al., 2006). In concordance with our previous study, we found that patients with right-sided MTLE performed worse in identifying a faux pas than patients with left-sided MTLE (Schacher, Winkler et al., 2006).

Furthermore, we used an animated fearful faces paradigm that reliably elucidates amygdalar BOLD activation in fMRI studies. Schacher et al. (2006) have previously shown that this paradigm results in bilateral amygdalar activation in the majority of healthy controls, whereas the activation is mostly contralateral to the side of seizure onset in patients with unilateral TLE (Schacher, Haemmerle et al., 2006). Once again we were able to demonstrate that the fearful faces fMRI paradigm is a reliable method for visualizing amygdala activation and lateralizing temporal lobe epilepsy. However, we found considerable variability of amygdalar activity. This is in accordance with T2 measurements in the amygdala demonstrating bilateral pathological changes even in patients with unilateral hippocampal sclerosis (Bartlett, Richardson, & Duncan, 2002).

Extending the findings of earlier studies, we aimed to investigate whether the asymmetry ratio of fMRI amygdalar activity was related to performance in the recognition of faux pas test. We found a weak but significant correlation between the asymmetry ratio of amygdalar activity and faux-pas test performance. A predominantly right-sided BOLD-signal of the amygdala during an animated fearful face paradigm was associated with better performance in the faux pas test.

Stepwise multiple regression analysis of our data revealed that the side of pathology, however, explained a more considerable part of the variance of faux pas test performance than the lateralization of the amygdala BOLD signal. Thus, patients with right-sided MTLE may be at increased risk for deficits in higher-order social cognition. Our findings are in line with previous studies of the effect of cerebral damage on ToM skills that support the view that ToM relies, at least in part, on the right hemisphere (Brunet et al., 2000; Calarge, Andreasen, & O'Leary, 2003; H. L. Gallagher et al., 2000; Griffin et al., 2006; Shamay-Tsoory, Tomer, & Aharon-Peretz, 2005; Siegal, Carrington, & Radel, 1996; Winner, Brownell, Happe, Blum, & Pincus, 1998), whereas unilateral amygdalar dysfunction per se is not sufficient to explain the variability of ToM task performance in our sample. Especially within the prefrontal structures, there seems to be a hemispheric lateralization, indicating that the right frontal lobe is more strongly associated with ToM abilities (Shamay-Tsoory, Tomer, Berger, Goldsher, & Aharon-Peretz, 2005; Stuss, Gallup, & Alexander, 2001; Vollm et al., 2006). Seizures which do have their onset in the temporal lobe will often invade extra-temporal structures in the course of the seizure (Jokeit et al., 1997; Oyegbile et al., 2004). Therefore, impairment of frontal lobe function may also be considered as a risk factor for deficits in higher-order ToM tasks in epilepsy (Farrant et al., 2005). However, other studies have found contradictory results with predominantly left hemisphere activation of the frontal lobe (Calarge et al., 2003;

Fletcher et al., 1995; Goel, Grafman, Sadato, & Hallett, 1995) or no effect of a hemispheric lateralization for ToM performances at all (Weed, 2008).

Post hoc analyses of separate subject groups showed that patients with right- but not left-sided MTLE presented a significant correlation between amygdalar signal asymmetry and faux pas test performance. Our results suggest that patients with right-sided MTLE, but more right-sided amygdalar reactivity tend to perform better than patients with right-sided MTLE and reduced amygdalar reactivity. Whereas the side of lesion explains the majority of variance in our sample, this specific correlation may suggest that ipsilateral amygdalar reactivity in patients with right-sided MTLE indicates the extension of epilepsy-related structural and functional pathology within a right hemisphere fronto-limbic network that governs affective and social processing.

Furthermore, the impaired performance on the advanced ToM task was not accounted for by variables such as age at seizure onset, duration of epilepsy or cognitive ability (as measured by IQ) and, thus, corroborate earlier findings that ToM abilities are mainly independent of other cognitive functions (Frith & Frith, 2003). However, we are aware that the present study did not specifically address the relationship between ToM and cognitive functions in TLE, elucidation of which requires more focused and exhaustive investigation. By contrast, age is supposed to have an influence upon faux pas test performance. We found a negative association with age. The effects of aging on ToM and their links with other cognitive processes, such as executive functions and memory, are still inconclusive. However, our finding is in accordance with recent studies, indicating that theory of mind abilities may decline with adult age (Duval, Piolino, Bejanin, Eustache, & Desgranges, ; Slessor, Phillips, & Bull, 2007).

There are some limitations of the study that need to be addressed.

A first remark concerns the weakness of the correlation between faux pas test performance and fMRI reactivity. Reasons include methodological limitations due to temporarily independent measurements of amygdalar activity and behavioral test performance as well as the imperfect reliability of both measures.

Second, due to the relatively small sample size, caution should be used, as the findings might not be transferable to the entire MTLE group. Therefore, it would be worthwhile to further study and isolate clinical characteristics within our subgroups of right- and left-sided MTLE patients.

In conclusion, right-sided MTLE, not unilateral amygdala dysfunction, can be considered as a primary risk factor for deficits in higher-order social cognition. At least in patients with

right-sided MTLE, ipsilateral amygdalar reactivity is related to social behavioural measures. Whether amygdala activation acts an unspecific indicator of the integrity of fronto-limbic circuitry or whether it is indeed involved in ToM processing needs to be investigated in patients who undergo amygdala resection for surgical treatment of epilepsy. Overall, our results support the hypothesis of a hemispheric lateralization for higher-order ToM performances.

ACKNOWLEDGMENTS

We would like to thank the Swiss Epilepsy Foundation for financial support and Gesa Osterkamp and Theresa Biesold for technical support. We also would like to thank Victoria Reed for valuable comments regarding the improvement of the manuscript.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DISCLOSURE

None of the authors has any conflict of interest to disclose.

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APPENDIX

At Fernhaven Elementary School, there was a story competition. Everyone was invited to enter. Several of the fifth graders did so. Christine, a fifth grader, loved the story she had entered in the competition. A few days later, the results of the competition were announced: Christine's story had not won anything, and a classmate, Jake, had won first prize. The following day, Christine was sitting on a bench with Jake. They were looking at his first prize trophy. Jake said, "It was so easy to win that contest. All of the other stories in the competition were terrible." "Where are you going to put your trophy?" asked Christine."

Questions:

1. "Did anyone say something they shouldn't have said or something awkward? If yes, who said something they shouldn't have said or something awkward? and why shouldn't he/she have said it or why was it awkward?"
2. "Did Jake know that Christine had entered a story in the contest?"
3. "How do you think Christine felt?"
4. "(Control question): in the story, who won the contest?"

5.3 Alterations in functional connectivity of the amygdale in unilateral mesial temporal lobe epilepsy

Sarah D. Broicher[1], Lars Frings[2], Hans-Jürgen Huppertz[1], Thomas Grunwald[1], Martin Kurthen[1], Günter Krämer[1], and Hennric Jokeit[1]

[1] Swiss Epilepsy Centre, Zürich, Switzerland

[2] Center of Geriatrics and Gerontology, Freiburg, Germany

Corresponding author:

Sarah D. Broicher, MSc

Swiss Epilepsy Centre

Bleulerstrasse 60, 8008 Zürich, Switzerland

Tel.: ++41/44/387-6348

Fax: ++41/44/387-6134

e-mail: Sarah.Broicher@swissepi.ch

Key words: mesial temporal lobe epilepsy, amygdala, fMRI, functional connectivity, theory of mind

ABSTRACT

The aim of this work was to evaluate the relationship between ipsilateral amygdala dysfunction in uni- lateral mesial temporal lobe epilepsy (MTLE) and remote temporal, frontal, and parietal brain structures and to identify their association with theory of mind (ToM) abilities. Functional magnetic resonance imaging (fMRI) data were acquired from MTLE patients with unilateral hippocampal sclerosis (n = 28; 16 left-sided) and healthy controls (HC, n = 18) watching an animated fearful face paradigm. To explore functional connectivity, we used independent component analysis (ICA) of fMRI data to characterize possible amygdala network alterations that may be caused by lateralized amygdala dysfunction. We furthermore investigated the relationship between activation within the amygdala network and ToM task performance. The pattern of amygdalar BOLD activation observed in response to an animated fearful face paradigm was bilateral amygdalar activation in HC and amygdala activation lateralized to the contralateral side in MTLE patients. In HC, a hemispheric asymmetry of the amygdala network was present with amygdala co-activation in predominantly left temporolateral and frontal brain structures. In MTLE patients, the observed asymmetry of amygdala connectivity was modulated by the side of pathology and the extent of amygdalar connectivity to the parahippocampal gyrus and insula was related to ToM test performance. These findings suggest that ipsilateral amygdalar dysfunction in MTLE is associated with altera- tions in remote temporal and frontal brain areas. The study of psychiatric and neurological disorders via network analysis allows for a shift of focus away from viewing dysfunctions of individual structures to a pathological network that pos- sibly gives rise to a variety of symptoms.

INTRODUCTION

Patients with mesial temporal lobe epilepsy (MTLE) are at considerable risk of developing psychiatric problems such as affective mood and personality disorders [16]. The extent of structural lesions in the mesiotemporal lobes, epileptogenic activity, age at onset of seizures, and etiology are among the multiple factors that can influence psychopathology in MTLE. Furthermore, given the importance of the limbic system in emotion processing and social cognition, it is not surprising that epileptogenic lesions capable of disrupting limbic connectivity are associated with a great variety of clinically significant behavioral abnormalities [6, 7, 20, 29].

We have recently shown that ipsilateral amygdalar dysfunction is present in the majority of MTLE patients, illustrating that functional pathology includes the amygdala as revealed by BOLD functional magnetic resonance imaging (fMRI) [28]. The amygdala has extensive connections with various neocortical areas in the prefrontal cortex and anterior temporal lobe as well as subcortical structures [1, 3, 14, 27, 30, 31]. Considering these interconnections, the amygdala emerges as a nodal point in a network that links together cortical and subcortical brain regions considered to be critically involved in emotion processing [26].

In MTLE patients with hippocampal sclerosis, reductions in both functional and structural connectivity between hippocampal structures and adjacent brain regions have been reported [13, 19, 34], whereas little is known about the functional connectivity of the amygdala in unilateral MTLE. Using a region-of-interest (ROI) approach, Vuilleumier et al. [33] have shown that structural amygdalar lesions lead to deafferentation in extrastriate visual cortical areas. This is strong evidence that the amygdala is capable of modulating processes in functionally and anatomically distant parts of the brain [11].

The purpose of our study is to evaluate the relationship between ipsilateral amygdala dysfunction and remote temporal, frontal, and parietal brain structures, known to be closely interconnected with the amygdala. We used independent component analysis (ICA), a new data-driven method that allows one to image connectivity of significant nodes of activity [10]. We hypothesized that MTLE patients show an altered amygdala network depending on the lateralization of their epilepsies. Accordingly, left- and right-sided MTLE (LMTLE, RMTLE) patients were expected to show primarily impaired ipsilateral connectivity, whereas contralateral connectivity should be less affected.

Moreover, we investigate whether amygdala connectivity is related to theory of mind (ToM) abilities, which were assessed using the recognition of Faux Pas Test in which MTLE

patients have previously been shown specifically to be impaired and which, among different validated tests, approved to be the most sensitive one for ToM deficits in MTLE [9, 29].

MATERIALS AND METHODS

Patients and healthy controls

A total of 28 consecutive patients with a diagnosis of unilateral medically refractory mesial temporal lobe epilepsy (MTLE) and unilateral hippocampal sclerosis, ipsilateral to epilepsy side (HS, 16 left-sided; 12 right-sided), admitted to the Swiss Epilepsy Centre between 2009 and 2010 were enrolled in this study (17 females; mean age 37.4 years+12.6 years; age range 16–60). Twenty-three patients were right-handed (self-reported), and fMRI indicated left-sided language dominance in all 5 left-handed patients. In all patients, the diagnosis of unilateral MTLE with partial and/or secondary generalized tonic-clonic seizures was based on typical clinical seizure semiology, interictal and ictal EEG findings and the results of MRI scans (see Table 1).

Table 1. Clinical data from MTLE patients.

Patient	Side of Seizure Onset	Sex	Handedness	Age	Mean Age at Epilepsy Onset in Years	Duration of Epilepsy in Years
1	Left	w	RH	43	19	24
2	Left	w	RH	17	13	4
3	Left	m	RH	32	4	28
4	Left	m	RH	19	17	2
5	Left	w	RH	45	41	4
6	Left	w	RH	36	1	35
7	Left	w	RH	35	22	13
8	Left	m	RH	30	11	19
9	Left	m	RH	33	17	16
10	Left	m	RH	42	24	18
11	Left	w	RH	45	9	36
12	Left	w	LH	49	35	14
13	Left	w	RH	18	4	14

Patient	Side of Seizure Onset	Sex	Handedness	Age	Mean Age at Epilepsy Onset in Years	Duration of Epilepsy in Years
14	Left	m	LH	35	4	31
15	Left	w	LH	44	9	35
16	Left	w	RH	16	10	5
17	Right	w	RH	30	7	23
18	Right	m	RH	60	43	17
19	Right	w	RH	48	15	33
20	Right	m	RH	34	8	26
21	Right	m	RH	48	28	20
22	Right	m	LH	47	32	15
23	Right	m	RH	53	3	50
24	Right	w	RH	44	34	10
25	Right	w	RH	17	1	16
26	Right	w	LH	25	22	3
27	Right	w	RH	45	4	41
28	Right	w	RH	58	27	31

All patients were therapeutically refractory to various first-line antiepileptic drugs (AEDs). None of the patients experienced a seizure in the 24-h period preceding the experimental session.

Eighteen right-handed (as assessed by the Edinburgh Handedness Inventory) [23], left-hemispheric dominant (as indicated by fMRI), native German-speaking participants with no history of psychiatric or neurological illness (confirmed by psychiatric clinical assessment) were enrolled (12 females; mean age 31.2 ± 5.8 years; age range 24–44). No abnormal findings on conventional brain MRI were observed in these controls.

The mean age of groups (MTLE, HC) did not differ significantly (ANOVA, n.s.), nor did gender distribution (Chi-square test, n.s.). LMTLE and RMTLE patients did not differ concerning age at epilepsy onset or duration of epilepsy (*t* test, n.s.). All subjects gave written informed consent. The study was approved by the local medical ethics committee and was in

compliance with the Declaration of Helsinki. Demographics and clinical characteristics are shown in Table 2.

Table 2. Demographic and behavioural data of HC, and LMTLE patients and RMTLE patients.

Variable	Healthy Controls (*n*=18) Mean (SD)	Left-sided MTLE Patients (*n*=16) Mean (SD)	Right-sided MTLE Patients (*n*=12) Mean (SD)	MTLE Patients (*n*=28) Mean (SD)
Sex (male; female)	6;12	6;10	5;7	11;17
Age in Years	31.22 (5.81)	33.69 (11.05)	42.42 (13.23)	37.43 (12.60)
MWT-B (estimated IQ)	113.22 (8.48)	92.25 (13.85)	96.75 (11.40)	94.18 (12.83)
Mean Age at Epilepsy Onset in Years		15.00 (11.27)	18.67 (14.17)	16.57 (12.48)
Duration of Epilepsy in Years		18.63 (11.78)	23.75 (13.30)	20.82 (12.48)
Faux-pas Test Total Score (0-20)	19.44 (0.92)	15.59 (2.60)	13.21 (3.26)	14.57 (3.09)

fMRI task design

The fMRI paradigm used here was first developed, validated, and applied to HC and patients with TLE by Schacher et al. [28]. Further information related to the selection procedure of the stimuli can be found in Schacher et al. [28]. The block-design paradigm consisted of eight activation and eight baseline blocks each lasting 24 s. The activation condition comprised 75 brief episodes (2–3 s) from thriller and horror films. All episodes showed the faces of actors who were expressing fear with high intensity. None of the episodes showed violence or aggression. During baseline blocks, 72 short episodes of similar length (2–3 s) with dynamic landscape video recordings were presented. Video clips of dull domestic landscapes were used owing to their stable low emotional content while their general visual stimulus properties were comparable to the movie clips. Frequency and duration of the sequences (2–3 s) were matched in the activation and control conditions. Stimuli were presented via a back-projection screen and viewed through a tilted overhead mirror. Prior to beginning, subjects were told that they would see rapid presentations of film sequences depicting fearful faces intermixed with landscape film sequences. They were instructed to relax while watching the film and to focus on the eyes of the actors during the activation blocks.

MRI acquisition

The structural and functional MRI data were recorded using a 3.0-Tesla Achieva scanner (Philips Medical Systems, Best, The Netherlands) between 2009 and 2010 using a standardized protocol. MRI sequences included T1-weighted spin-echo and gradient-echo three-dimensional multiplanar reconstruction images (MPRAGE) with (patients) and without (healthy controls) intravenous contrast application, coronal T2-weighted turbo spin echo, T2-weighted fast-fluid attenuated inversion recovery (FLAIR) and diffusion-weighted sequences. Coronal T2 and FLAIR slices were 2–3 mm thick and were acquired at 90° perpendicular to the long axis of the hippocampus. Subjects were sited in the head coil with ear pads and foam padding to minimize head motion. There were successive parameters for the anatomic sequence: 176 axial slices with 1-mm single-slice thickness, repetition time (TR) 8.2 ms, echo time (TE) 3.93 ms, 8° flip angle, field of view (FOV) 250 mm, and 288 x 288 matrix.

Functional data were acquired using EPI T2*-weighted sequences. The following parameters were applied to measure amygdalar activation: 18 coronal slices, 4-mm slice thickness (interslice gap: 0 mm), TR 1,500 ms, TE 35 ms, 75° flip angle, FOV 220 mm, matrix size 64 x 64 (voxel size 3 x 3 x 3 mm), reconstructed into an image matrix of 128 x

128. Coronal slices were geared orthogonally to the hippocampal formation and covered most of the temporal and frontal lobes. Ten ‘‘dummy’’ scans were first acquired to reach steady-state magnetization and discarded.

fMRI data analyses

fMRI single subject data analyses were performed using the SPM8 software package (http://www.fil.ion.ucl.ac.uk) running on MATLAB R2009b (http://www.mathworks.com). We used two different types of analytical techniques for fMRI data.

We first applied a classical, model-driven approach where specific hypothesis about the expected blood-oxy- gen-level-dependent (BOLD) response at the individual voxel locations are tested using a general linear model (GLM). This analysis was used to functionally define regions-of-interest (ROI) in the amygdala that show the typical activation and deactivation pattern in response to dynamic fearful faces and reduced ipsilateral amygdala reactivity in the majority of patients with unilateral MTLE. In a second step, independent component analysis (ICA) was conducted, which is a hypothesis-free, data-driven approach, aimed at identification of a network of functionally connected brain regions that included the amygdala. This network will be referred to as the ‘amygdala network’ for brevity.

Preprocessing

Data were preprocessed with (1) realignment of all images to correct for head movement during functional MR scanning using six parameter rigid-body transformations; (2) coregistration to obtain an overlap between functional images and the anatomical image; (3) normalization of the resulting images to match the Montreal Neurological Institute (MNI) template brain in Talairach-space and resampling to 3 x 3 x 3 mm^3. Images were additionally spatially smoothed with a Gaussian kernel of 4 x 4 x 4 mm^3 full width at half-maximum.

General linear model (GLM) analysis

Single-subject analysis: For each subject, fMRI responses were modeled using a canonical hemodynamic response function and the general linear model was used to perform a first level, within-subjects analysis on the functional data from each subject individually for the primary contrast ‘fearful faces minus landscape’, with spatial realignment parameters entered as covariates. Before model estimation, data were band-pass filtered (high-pass filter: 128 s, low- pass filter: hemodynamic response function) to remove high- and low-frequency noise. The overall model fit was assessed using an *F* statistics. A statistical parametric map of

brain activation was computed representing the contrast 'fearful faces minus landscape'. Results were taken to a second level group analysis.

Group level analysis: To identify the main effect of task for each study group, we used one-sample *t* tests. Mean activation and deactivation patterns were obtained to visualize group-level activation maps that were generated with a global threshold set at $p < 0.001$ following correction for multiple comparisons on a whole-brain level family-wise error (FWE) basis, and a cluster extent (kE) threshold set at 5 voxels.

Independent component analysis (ICA)

Functional connectivity analyses were performed using the group ICA of fMRI (GIFT) toolbox (http://mialab.mrn.org/software/gift/) running on MATLAB R2009b. ICA is a multivariate data-driven decomposition method whose application on functional imaging data is relatively new and constitutes an alternative method to classical model-driven analyses of fMRI data [10]. ICA allows for separation of independent 3D spatial maps based on the characteristic signal time course of the voxels grouped together to form the respective spatial map. In that sense, ICA is commonly referred to as decomposing time series data into maps of voxels which display a mutual functional connectivity; i.e., brain regions whose activity over time follow an identical, or similar, time course are interpreted to represent a network of functionally connected brain regions.

Preprocessed fMRI time series data were subjected to a group spatial ICA for the identification of spatial, independently distributed component networks. Analysis steps were carried out with default settings and comprised group data reduction by means of a principal component analysis, ICA calculation using an infomax algorithm, and back-reconstruction in order to obtain individual independent component maps [10].

The amygdala network was selected from the ICA-calculated, group-averaged components by two independent, experienced raters (S. B., L. F.). The selected component was the only component that involved the amygdalae and was selected by visual inspection of the respective component maps overlayed on the group-averaged T1-weighted image. The identified component not only included the amygdalae but was centered on the amygdalae, i.e., highest levels of connectivity were observed within the amygdalae.

Individual amygdala network maps were then taken to second level analyses performed with SPM8. In order to reveal the amygdala network in each group, separate one-sample *t* tests were computed. Group differences within the amygdala network were then assessed in a subsequent two-way analysis of covariance (ANCOVA). Fixed factors included group

(LMTLE, RMTLE, HC) and sex. Control variables were age, age at epilepsy onset, duration of epilepsy, and IQ. Significant differences between groups were assessed using *t* contrast maps, restricted to the amygdala network of HC by inclusive masking.

Behavioural data

All participants performed a multiple-choice vocabulary test (MWT-B), which served an estimate of crystalline verbal intelligence [18] as well as a shortened version of a Faux Pas Test [32] that comprised five selected stories. Patients were asked to read each story silently, knowing that they would then be asked questions about the story. The first question concerned the detection and comprehension of the faux pas, while questions two, three, and four required the patient to impute the mental state of and attribute emotions to another agent. Further information related to the test can be found in Schacher et al. [29].

Data analysis involved the sum of the first four questions, where each question was scored with one point, resulting in a maximum of twenty points for all five stories. Points for the control question were excluded from the total score, but served as an indicator of text comprehension.

Relationship between amygdala network and behavioural data

A two-way ANCOVA with the fixed factors group (LMTLE, RMTLE, HC) and sex and the covariates Faux Pas Test performance, age, age at epilepsy onset, duration of epilepsy, and IQ was performed to determine significant differences between the groups in the involvement of amygdala network nodes for Faux Pas Test performance. Again, significant differences between groups were assessed using *t* contrasts that were masked with an image of the amygdala component of HC.

RESULTS

Main BOLD effects (general linear model, GLM)

Task-related activation patterns: mean activation across HC in response to fearful faces was observed in bilateral hippocampus, amygdala, precentral gyrus, inferior frontal gyrus (IFG), and insula as well as in the right middle temporal gyrus (MTG) and left thalamus. By contrast, group-wise activation in LMTLE patients was observed contralateral to the lesion, in right hippocampus, amygdala, precentral gyrus, IFG, MTG, fusiform gyrus, medial temporal pole (TP), and pallidum. In contrast, mean activation in RMTLE patients was found

contralateral to the lesion, in the left amygdala, hippocampus, superior temporal gyrus/ sulcus (STG/STS), and ipsilateral in the right IFG (see supplementary table and figure).

Connectivity analysis of amygdalar BOLD responses (independent component analysis, ICA)

Amygdala connectivity: ICA analysis identified a set of six clusters significantly co-activated with bilateral amygdala BOLD activity in HC (thresholded at $p<0.001$, uncorrected, k=5 contiguous voxels) (see Table 3; Fig.1, red). Besides the two larger clusters centered around the bilateral amygdalo-hippocampal transition area, the amygdalae and hippocampi were found to be co-activated with the left TP, the left IFG, left superior medial frontal gyrus (SMFG), left anterior cingulate cortex (ACC), left MTG and right cerebellum. All peak voxels in this analysis survived a threshold of $p<0.05$ (FDR corrected).

Group differences in amygdala connectivity: A two-way ANCOVA with the fixed factors group (LMTLE, RMTLE, HC) and sex and the covariates age, age at epilepsy onset, duration of epilepsy, and IQ were calculated in order to detect group differences within the amygdala component. Group contrasts revealed significantly reduced amygdalae co-activation in RMTLE patients compared to HC on the contralateral side in the left hippocampus, TP, and ACC (see Table 1; Fig. 1, blue). LMTLE patients also showed reduced amygdala co-activation in the left hippocampus, the left STG/STS, and the right IFG (see Table 3; Fig. 1, green). RMTLE patients compared to LMTLE patients showed reduced amygdalae co-activation within the right medial TP, right MTG and left IFG (see Table 3; Fig. 1, yellow), whereas LMTLE patients compared to RMTLE patients showed no reduced amygdala connectivity.

Table 3. Brain regions co-activated with the amygdala in HC, LMTLE patients and RMTLE patients.

	HC (*n*=18) Mean (SD)		LMTLE Patients (*n*=16) Mean (SD)		RMTLE Patients (*n*=12) Mean (SD)		Difference between groups
Region	Peak MNI coordinates [x y z]	*t*	Peak MNI coordinates [x y z]	*t*	Peak MNI coordinates [x y z]	*t*	
R amygdalo-hippocampal area (1)	+21 -10 -17	22.51					
L amygdalo-hippocampal area (2)	-24 -13 -17	17.38	-33 -25 -17	3.83	-24 -13 -17	3.79	RMTLE, LMTLE < HC
L temporal pole (3)	-57 +6 -6	7.71			-54 +5 -5	3.88	RMTLE < HC
R medial temporal pole					+45 +5 -26	3.93	RMTLE < LMTLE
L inferior frontal gyrus (3)	-57 +17 +28	7.34			-45 +11 -6	5.04	RMTLE < LMTLE
R inferior frontal gyrus			+54 +6 +34	4.20			LMTLE < HC
L middle temporal gyrus (3)	-60 -10 -17	4.28					
R middle temporal gyrus					+48 +2 -29	3.95	RMTLE < LMTLE
L superior temporal gyrus			-57 -1 -6	3.90			LMTLE < HC
L anterior cingulate cortex (4)	-8 +20 +28	9.29			-3 +17 +31	4.34	RMTLE < HC
L superior medial frontal gyrus (5)	-6 +66 +34	6.91					
R cerebellum (6)	+18 -49 -47	7.44					

Coordinates (x y z) are given in MNI space. For ANCOVA, *t* contrast maps were masked with an image of the amygdala component of healthy controls, all $p<0.001$, k=5 contiguous voxels. Number in brackets corresponds to cluster number.

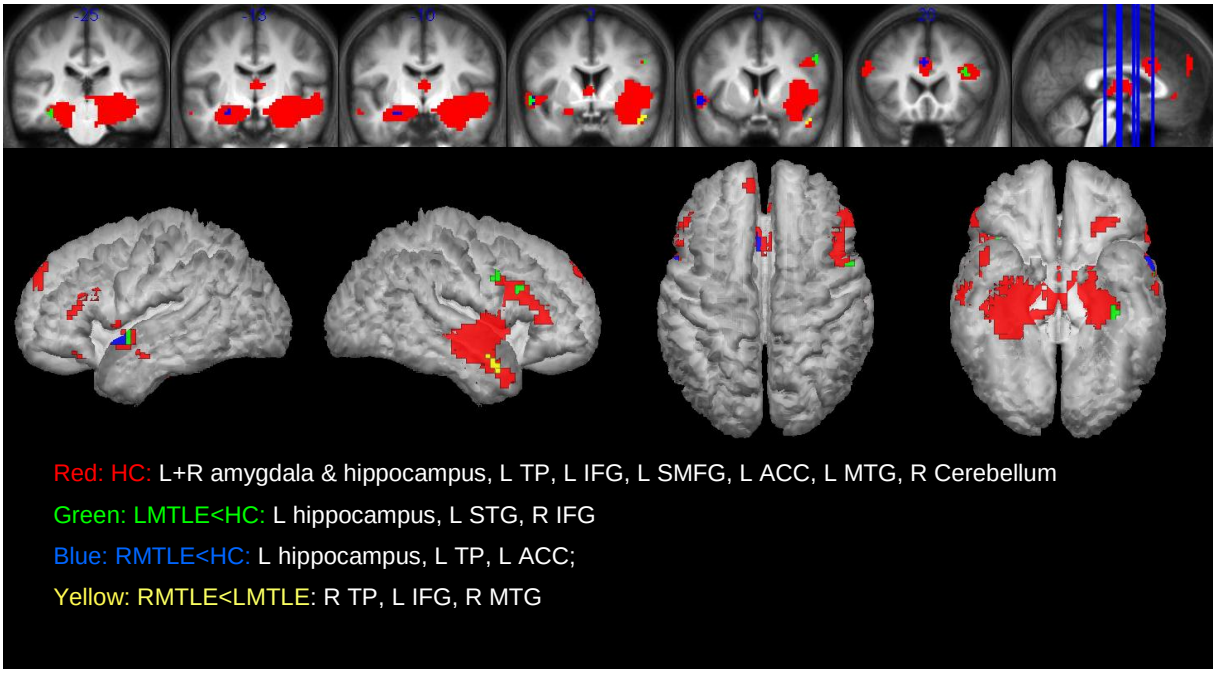

Figure 1. Amygdala network in healthy controls (HC) and left- and right-sided mesial temporal lobe epilepsy patients (LMTLE, RMTLE), overlaid on a mean anatomical scan of all subjects (L=Left side; R=Right side). Amygdalae co-activation with both hippocampi, left temporal pole, left inferior frontal gyrus, left superior medial frontal gyrus, left anterior cingulate cortex, left middle temporal gyrus and right cerebellum of the HC group (red) (p<0.001, uncorrected). Significantly reduced amygdala co-activation in LMTLE (green) and RMTLE patients (blue) compared to HC (red), and in RMTLE patients compared to LMTLE patients (yellow) (p<0.001, uncorrected; k=5 contiguous voxels).

Behavioural data

To directly compare the Faux Pas Test results of MTLE patients with those of HC, we analysed the fixed factors group (MTLE, HC) and sex in a two-way ANCOVA with the covariate age and IQ. Only the factor group influenced the test performance: MTLE patients performed worse than HC [F(1, 40)=20.51; p<0.001; eta^2=0.34; power=0.99]. No significant influence of the factor sex or age was noted (p>0.05).

In a next step, we analysed the MTLE group in more detail by investigating the influence of the side of epilepsy using a two-way ANCOVA with the fixed factors side of epilepsy, sex, and the covariates age, age at seizure onset, duration of epilepsy, and IQ. Patients with RMTLE performed worse than patients with LMTLE [F(1, 20)=12.30; p<0.002; eta^2=0.39; power=0.93]. Again, no significant influence of the factor sex or any of the covariates was found (p>0.05).

Relationship between amygdala network and behavioural data

Faux Pas Test performance of HC was not included in this analysis due to reduced variance and a strong ceiling effect in this group.

To investigate the relationship between activation in the amygdala network and Faux Pas Test performance in LMTLE and RMTLE, we performed a two-way ANCOVA with the fixed factors group (LMTLE, RMTLE) and sex and overall Faux Pas Test performance, age, age at epilepsy onset, and duration of epilepsy as covariates. Group contrasts were masked with an image of the amygdala component of HC and revealed that in LMTLE patients better Faux Pas Test performance was associated with increased activation in the contralateral insula (x y z coordinates=+39 -7 -8; see Fig. 2a, green) whereas in RMTLE patients, the contralateral hippocampal formation including the amygdala (x y z coordinates=-21 -25 -23; see Fig. 2b, blue) was related to overall Faux Pas Test performance (t=2.53, thresholded at p<0.01, k=5 contiguous voxels). There was no significant influence of the factor sex or any of the covariates (p>0.05).

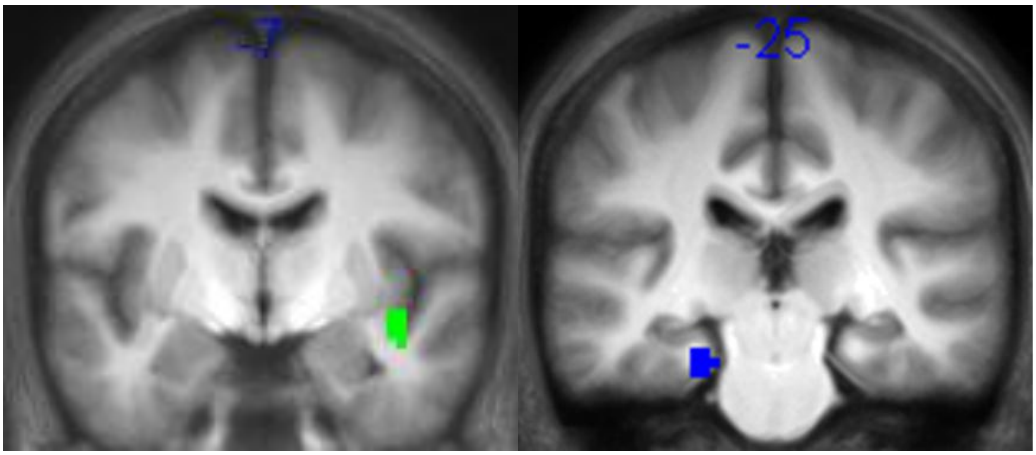

Figure 2. Relationship between amygdala network and ToM task (faux pas test) in left-sided (Fig. 2a; green) and right-sided mesial temporal lobe epilepsy patients (LMTLE, RMTLE) (Fig. 2b; blue), overlaid on a mean anatomical scan of all subjects (L=Left side; R=Right side).

DISCUSSION

Main results

We explored connectivity of the amygdala with various temporal, frontal, and parietal brain areas in patients with unilateral MTLE.

There were three main findings: (1) we found the typical amygdalar BOLD activation in response to an animated fearful-faces paradigm: bilateral amygdalar activation in HC and amygdala activation lateralized to the contralateral side in MTLE patients; (2) in HC, a

hemispheric asymmetry of the amygdala network was present with amygdala co-activation predominantly in the left temporolateral and frontal brain structures, whereby in MTLE patients the observed asymmetry of amygdala connectivity was modulated by lateralization of side of seizure onset; (3) the level of connectivity was related to Faux Pas Test performance.

In previous studies [8, 28] we were able to show that the animated fearful-faces paradigm results in bilateral amygdalar activation in HC and amygdala activation lateralized to the contralateral side of seizure onset in the majority of MTLE patients. In the present study, we replicated this finding identifying symmetrical activation pattern within HC and a corresponding asymmetrical activation pattern within MTLE patients. Our analysis of functional connectivity of the amygdala was based on this prior identification of a main effect of task in each study under investigation.

The amygdala network in HC and MTLE patients

The amygdala network, activated by the applied stimulus material in HC, was found to be asymmetrically organized within different temporal and frontal lobe brain structures. A left predominance was observed in the TP, IFG, SMFG, ACC, and MTG. Furthermore, we found crosswise co- activation within the right cerebellum.

Whether this asymmetry reflects certain task or stimulus properties or brain hemispheric asymmetry cannot be answered by our study. However, this left predominance of connectivity is in line with previous structural data showing leftward asymmetry in parietotemporal white matter as well as the fiber density of the arcuate fasciculus in subjects with left-sided speech dominance [15, 22, 25]. Moreover, predictions of language lateralization have been demonstrated from gray matter probabilistic maps of high-resolution structural scans [17] as well as from white matter by means of diffusion tensor imaging [12]. Additionally, recent resting state fMRI studies reported a left predominance in basal functional connectivity within the medial temporal lobe network in HC [5] and more pronounced effects of impaired functional connectivity ipsilateral to the seizure focus in LMTLE patients compared to RMTLE patients [24].

We found a clear effect of lesion, whereby this effect of pathology was most prominent in brain areas showing greater connectivity. In MTLE patients, the observed asymmetry of amygdala connectivity was modulated by lateralization of side of seizure onset. Compared to HC, we found reduced amygdala co-activation in the left hippocampus, the left STS, and the right IFG in LMTLE patients whereas RMTLE patients showed reduced connectivity in the left hippocampus, the left TP, and the left ACC. Thus, we did not find the expected

impairment of ipsilateral connectivity in RMTLE patients, which suggests that despite only unilateral morphological MRI-proven pathology exists, the contralateral hemisphere may also be involved through transcallosal projections [27].

Which nodes within the amygdala network are associated with ToM performances?

We further investigated ToM performance in MTLE patients using the Faux Pas Test. The results of the present study support our previous finding that patients with MTLE, especially those with right-sided seizure onset, show impairments in the recognition of faux pas [29]. This observation is also in accordance with our finding that RMTLE patients, compared to LMTLE patients, had significantly reduced amygdala-coactivation within the ipsilateral medial TP and the MTG. Further, compared to HC, the contralateral activation in the amygdalo-hippocampal area, in addition to other structures, was observed to be significantly reduced in RMTLE patients. Thus, RMTLE patients were found to have functional disturbances in both amygdalo-hippocampal areas: the left as revealed by reduced co-activation as well as the right, due to ipsilateral mesiotemporal pathology. This may be an explanatory factor underlying their especially poor performance in the ToM test. At the behavioral level, pronounced difficulties in RMTLE patients have also been reported for facial emotion recognition abilities [20, 21]. Extending the findings of our earlier studies [29], we investigated in the present study which structures within the amygdala network are related to ToM test performance. In patients with LMTLE, connectivity within the contralateral insula, a limbic-related cortical area known to have widespread reciprocal connections to the amygdala and hippocampus [2, 31], was related to Faux Pas Test performance. In RMTLE patients connectivity within the contralateral hippocampal formation, including amygdala, was related to the behavioral data.

Our results suggest that the integrity of contralateral mesiotemporal lobe structures play a more important role in MTLE patients for performance on a ToM task than remaining spatially connected ipsilateral activity. This result may be indicative for compensatory activation of the contralateral mesiotemporal region [5]. However, since no comparison was performed with controls, no final conclusion can be drawn regarding the relationship between ToM and MTLE.

There are some limitations of the study that need to be addressed. First, the degree of hippocampal atrophy was not controlled in this study. Second, extension of structural mesial temporal lobe lesions may exceed the ipsilateral hippocampus and may also be found in ipsilateral or even bilateral amygdala. Accordingly, amygdala T2 measurements demonstrated

bilateral pathological changes even in patients with unilateral hippocampal sclerosis [4]. Finally, methodological limitations may exist due to temporarily independent measurements of amygdalar activity and behavioral test performance that can be avoided in forthcoming studies.

Conclusion and future perspectives

The amygdala network in HC was found to be asymmetrically organized within various temporal and frontal lobe brain structures, whereby in MTLE patients the observed asymmetric pattern of amygdala connectivity was strongly modulated by pathology. These findings suggest that ipsilateral amygdalar dysfunction in MTLE patients may result in loss of functional connectivity of brain structures remote to but interconnected with the amygdala.

The use of functional connectivity analysis in psychiatric and neurological disorders as well as in epilepsy surgery patients may allow a broader view, away from the roles and dysfunctions of individual regions of the brain, towards a perspective in which affective symptoms and deficits in social cognition may be seen as symptom domains arising from certain pathological networks.

Acknowledgements

We would like to thank the Swiss Epilepsy Foundation for financial support and Dr. Dominik Huber, Gesa Osterkamp, and Theresa Biesold for technical support.

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Supplementary Table. Main effects of emotion: fearful faces > landscape / SPM peaks of activation for each group.

	HC (*n*=18) Mean (SD)		LMTLE Patients (*n*=16) Mean (SD)		RMTLE Patients (*n*=12) Mean (SD)	
Region	Peak MNI coordinates [x y z]	*t*	Peak MNI coordinates [x y z]	*t*	Peak MNI coordinates [x y z]	*t*
R hippocampus	+27 -13 -11	8.24	+27 -13 -8	6.73		
L hippocampus	-30 -10 -17	6.68			-30 -10 -14	3.59
R amygdala	+27 -13 -11	8.24	+24 -4 -17	7.04		
L amygdala	-18 -10 -17	6.32			-15 -25 -8	5.42
R precentral gyrus	+54 +5 +40	9.39	+54 +8 +37	4.81		
L precentral gyrus	-48 -1 +31	6.23				
R inferior frontal gyrus	+54 +23 +4	7.22	+48 +32 +4	6.70	+61 +23 +16	4.53
L inferior frontal gyrus	-45 +11 +25	4.59				
(R insula) / R middle temporal gyrus	+54 -21 -8	6.19	+48 -25 -2	6.35		
L insula lobe	-27 +26 +4	6.12				
L middle temporal gyrus					-51 -16 -14	4.84
L thalamus	+18 -16 +10	3.69				
R fusiform gyrus			+36 -7 -35	4.96		
R medial temporal pole			+36 -1 -29	3.94		
R pallidum			+27 -7 +7	4.40		

Coordinates (x y z) are given in MNI space. For *t*-test contrasts, all $p<0.001$, k=5 contiguous voxels.

5.4 fMRI response of dysplastic amygdala in patients with mesial temporal lobe epilepsy

Broicher S[1], Kuchukhidze G[2], Grunwald T[1], Krämer G[1], Kurthen M[1], Trinka E[2], Jokeit H[1]

1 Swiss Epilepsy Center, Zürich, Switzerland

2 Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

Corresponding author:

Sarah Broicher, MSc

Swiss Epilepsy Center

Bleulerstrasse 60, 8008 Zürich, Switzerland

Tel.: ++41/44/387-6348

Fax: ++41/44/387-6134

e-mail: Sarah.Broicher@swissepi.ch

Key words: amygdala, cortical dysplasia, epilepsy, fMRI

1. Introduction

The amygdala-complex is considered to be a pivotal component of processing of stimuli with emotional and social significance [1, 2]. It modulates neuronal systems in response to perception of such stimuli which govern cognitive and social behavior [3]. Dysfunction of the human amygdala has been implicated in disturbances of memory, attention, impaired ability to evaluate emotional situations, autism, depression, narcolepsy, posttraumatic stress disorders and phobias [4]. Amygdalar lesions are associated with epilepsy, Alzheimer's disease [5], schizophrenia [6] and Urbach-Wiethe syndrome, a rare genetic disorder with calcified amygdalae [7].

In patients with mesial temporal lobe epilepsy (mTLE), amygdalae are often part of the epileptogenic zone and, in about a quarter of patients with hippocampal sclerosis (HS), the ipsilateral amygdala shows volume reduction or even atrophy [4, 8]. In addition, an association has been observed between epilepsy duration and the extent of amygdala volume loss [9].

A dysplastic amygdala may present with increased volume and high MR signal in T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences [10]. Similar MRI features are common in limbic encephalitis affecting mesio-temporal regions [11, 12]. However, in the majority of cases they present with initial swelling of the mesio-temporal area with subsequent evolution from signal increase and enlargement to atrophy over several months [12, 13].

Another cause of mesio-temporal volume increase and high MR signal in T2 and FLAIR could be a high grade glial tumor characterized by contrast enhancement and progression over time. Low grade glial tumors are the most challenging to differentiate from dysplasia, since they are not frequently enhanced by contrast and remain stable over a long period of time.

Functional organization of cortical dysplasias and other malformations of cortical development (MCD) have been assessed non-invasively by functional MRI (fMRI) and different patterns of fMRI activity have been observed: MCD caused by disturbances of cortical organization showed activity during simple motor tasks, whereas in MCD due to disturbances of earlier steps of cortical development, e.g. cortical dysplasia Palmini type II [14], activity was shifted to unaffected cortical areas in over 50% of patients [15].

fMRI studies have demonstrated a major role of the amygdala in the processing of emotions by responsivity to fearful facial expressions [16, 17]. In contrast to static photographs [16], an animated fearful face paradigm [17] activated the amygdalae bilaterally

in all 17 healthy controls, whereas the majority of patients (11 out of 12) with unilateral temporal lobe epilepsy (TLE) and HS showed amygdalar activation contralateral to the seizure onset side.

However, in some patients, dissociation between amygdalar activations and epileptogenic lesion were found [17]. In two patients ipsilateral amygdala activity and reversed asymmetries in parahippocampal activations were observed.

Here, we investigate for the first time, whether amygdalar response in fMRI is principally impaired if it is affected by dysplasia as defined by stationary but increased volume in T1- and signal enhancement in T2-weighted and FLAIR MRI sequences.

2. Methods

2.1. Participants

Twenty-five patients aged 16 to 60 (mean 38 years, SD 13.2; 13 men, 12 women; 24 right handed and 1 ambidexter) with TLE (mean age at seizure onset 15.2 years, SD 12.7 and epilepsy duration 23.1 years, SD 13.7) were investigated (see Table 1). Patients were recruited from consecutive inpatient admissions to the Swiss Epilepsy Center.

All patients underwent neurological examination and routine EEG recordings using the 10-20 system. Seizure types and epilepsy syndromes were diagnosed according to the classification of the International League Against Epilepsy [18, 19]. Seizure onset zone was determined by continuous interictal and ictal video/EEG monitoring with scalp and sphenoidal electrodes.

Twenty-four patients had mTLE and one had neocortical TLE with cavernoma localized in the lateral temporal lobe as well as ipsilateral HS and pDA. Eighteen patients had HS (17 unilateral and one bilateral). All patients had pharmacoresistant epilepsy (14/25 patients had daily or weekly seizures) (see Table 1).

Table 1
Demographic, epilepsy, MRI and fMRI data of 25 patients with temporal lobe epilepsy.

Patients	Sex	Age	Age at seizure onset [y]	Duration of epilepsy [y]	Seizure frequency[a]	Side of seizure onset	Morphologic lesion	Amygdala activation	LI	*p*-Value	Language	Handedness (right/left)
1	m	46	29	17	M	Right	HS	Unilat. left	1	0.05	Left	RH
2	w	46	14	32	M	Right	HS	Unilat. left	1	0.001	Left	RH
3	m	33	8	25	D	Right	HS	Unilat. left	1	0.001	Left	RH
4	m	56	42	14	W	Right	HS	Unilat. left	1	0.01	Left	RH
5	m	53	2	51	M	Right	HS	Right > left	−0.51	0.001	Bilateral	Ambidexter
6	m	43	37	6	W	Right	HS	Unilat. left	1	0.01	Left	RH
7	w	57	27	30	M	Right	HS	Bilateral	−0.10	0.01	Bilateral	RH
8	w	25	21	4	W	Right	HS; pDA	Unilat. left	1	0.001	Left	RH
9	w	48	7	41	M	Right	HS; AA	Right > left	−0.74	0.05	Left	RH
10	m	26	26	3	W	Right	pDA	Unilat. left	1	0.001	Left	RH
11	w	44	3	41	W	Right	HS; FCD frontobasal	Unilat. left	1	0.001	Left	RH
12	m	47	10	37	M	Right	HS; arachnoid cyst temporo-polar left	Left > right	0.49	0.001	Left	RH
13	w	60	45	15	M	Right	Small cystic lesion adjacent to right amygdala	Bilateral	−0.13	0.05	Left	RH
14	w	29	6	23	M	Right	HS; cavernoma temporal	Bilateral	0.11	0.01	Left	RH
15	w	42	19	23	D	Left	HS	Unilat. left	1	0.001	Left	RH
16	w	30	11	19	D	Left	HS	Unilat. right	−1	0.001	Left	RH
17	m	35	2	33	D	Left	HS	Right > left	−0.82	0.001	Left	RH
18	m	16	4	12	D	Left	HS	Bilateral	−0.24	0.001	NA	RH
19	w	49	5	44	M	Left	HS	Unilat. right	−1	0.001	Left	RH
20	w	45	9	36	D	Left	HS	Unilat. right	−1	0.001	Left	RH
21	m	32	5	27	W	Left	HS; pDA	Right > left	−0.67	0.01	Left	RH
22	m	41	23	18	M	Left	HS; pDA	Bilateral	−0.01	0.01	Left	RH
23	m	17	4	13	W	Left	HS; ulegyria occipital	Unilat. right	−1	0.001	Left	RH
24	m	21	11	10	W	Bilateral	HS; AA	NA	0	NA	Left	RH
25	w	16	12	4	M	Left	HS; pDA; cavernoma temporolateral	Left > right	0.82	0.001	Left	RH

m – man, w – woman, y – years, M – monthly, D – daily, W – weekly, HS – hippocampal sclerosis, pDA – probable dysplastic amygdala, AA – amygdala atrophy, FCD – focal cortical dysplasia, unilat. – unilateral, LI – lateralization index, NA – not applicable.
[a] Seizure frequency at the time of fMRI test.

Language laterality was determined either by use of an fMRI paradigm employing a verbal fluency task [17] (n=23) or by Wada test if the fMRI was inconclusive (n=2) [20]. The majority of patients (23/25) had left-sided language dominance, two had bilateral language representation. Handedness was determined by the Edinburgh Handedness Inventory.

Every patient gave written informed consent after a complete explanation of the study. The present study was performed in adherence to the Declaration of Helsinki and was also approved by a local medical ethics committee.

2.2. fMRI task design

The fMRI paradigm used here was first developed, validated and applied to healthy controls and patients with TLE by Schacher *et al.* [17]. Further information related to the selection procedure of the stimuli can be found in Schacher *et al.* [17]. The block design paradigm consisted of eight activation and eight baseline blocks each lasting 24 seconds. The activation condition comprised 75 brief episodes (2 to 3 seconds) from thriller and horror films. All episodes showed the faces of actors who were expressing fear with high intensity. None of the episodes showed violence or aggression. During baseline blocks 72 short episodes of similar length (two to three seconds) with dynamic landscape video recordings were presented. Video clips of dull domestic landscapes were used owing to their stable low

emotional content while their general visual stimulus properties were comparable with the movie clips. Frequency and duration of the sequences (2 to 3 seconds) were matched in the activation and control conditions. Stimuli were presented via a back-projection screen and viewed through a tilted overhead mirror. Prior to beginning, subjects were told that they would see rapid presentations of film sequences depicting fearful faces intermixed with landscape film sequences. They were instructed to relax while watching the film and to focus on the eyes of the actors during the activation blocks.

2.3. MRI acquisition

The fMRI-data were recorded using a 3.0 Tesla Achieva scanner (Philips Medical Systems, Best, The Netherlands) between 2007 and 2009 using a standardized protocol. MRI sequences included T1-weighted spin echo and gradient echo three-dimensional multiplanar reconstruction images (MPRAGE) with and without intravenous contrast application, coronal T2-weighted turbo spin echo, T2-weighted fast fluid attenuated inversion recovery (FLAIR) and diffusion weighted sequences. Coronal T2 and FLAIR slices were 1-3 mm thick and were acquired at 90° perpendicular to the long axis of the hippocampus. Subjects were sited in the head coil with ear pads and foam padding to minimize head motion. There were successive parameters for the anatomic sequence: 176 axial slices with 1-mm single-slice thickness, repetition time (TR) 8.2 milliseconds, echo time (TE) 3.93 milliseconds, 8° flip angle, field of view (FOV) 250 mm, and 288 X 288 matrix.

Functional data were acquired using EPI T2*-weighted sequence. The following parameters were applied to measure amygdalar activation: 18 coronal slices, 4-mm slice thickness (interslice gap: 0 mm), TR 1500 milliseconds, TE 35 milliseconds, 75° flip angle, FOV 220 mm, matrix size 64 X 64 (voxel size 2.75 X 2.75 X 4 mm), reconstructed into an image matrix of 128 X 128. Coronal slices were geared orthogonally to the hippocampal formation and were spread over the anterior temporal lobe.

2.4. Data analyses

fMRI single subject data analysis was performed with BrainVoyager QX (BrainInnovation, Maastricht, the Netherlands). In the primary analyses the data were preprocessed with 1) three-dimensional motion correction and 2) trend removal by temporal fast Fourier transform-based high-pass filtering and transformed into Talairach co-ordinate

area. Images of the fearful face task were additionally spatially smoothed with a full width at half-maximum of 4 mm.

For multiple regression analysis a general linear model (GLM) with the predictor for the activation condition was computed. The time courses of the predictor were obtained by using a linear model of the hemodynamic response. The overall model fit was assessed using F statistics. Significant differences between the experimental conditions were assessed using contrast (*t*) maps.

For images in the fearful face task, individual volumes of interests (VOIs) were defined for the amygdalar region. VOIs were specified functionally for each patient separately using a predefined statistical threshold of $p < 0.05$; $p < 0.01$ and $p < 0.001$ (see Table 1). Anatomic borders of the functional clusters were the uncal recess caudally and the optical chiasm rostrally and white matter superiorly. For each VOI the number of activated voxels was counted in the left and right hemisphere at the lowest reasonable statistical threshold. Lateralization indexes (LI) were defined for the number of meaningful activated voxels in the amygdalar/periamygdalar area using the formula: LI = (left - right)/(left + right). LI between ±0.5 and ±1 was defined to represent strong lateralization and LI between ±0.25 and ±0.5 – weak lateralisation (with "–" lateralizing to the right and "+" to the left, respectively). LI between -0.25 and +0.25 was defined as bilateral amygdalar activation.

2.5. Criteria for the assessment of amygdalar structural abnormalities

MRIs were assessed to detect and categorize amygdalar structural abnormalities by two independent raters from different institutions (SB - Swiss Epilepsy Center, Switzerland and GK – Department of Neurology, Innsbruck Medical University, Austria). The raters were blinded with regard to clinical data.

Amygdalae were assessed visually for size (T1-weighthed MPRAGE sequence) and MR signal intensity (T2 and FLAIR sequences). Amygdalae were considered "lesional" if the combination of size and signal abnormalities were observed. Size was assessed in comparison to the contralateral side and was considered abnormal if it was atrophic or pathologically increased. Amygdalar lesions were categorized as:

(1) amygdala atrophy (AA) if it was shrunken (atrophic) with signal increase in T2 and FLAIR sequences;

(2) probable dysplasia (pDA) if the size was pathologically increased with signal increase in T2 and FLAIR sequences; additional MRI features of pDA were white matter volume

reduction and increased signal in T2 and FLAIR sequences in ipsilateral temporal lobe; in order to exclude limbic encephalitis the patients should not have had MRI features of swelling at the initial MRI performed at the manifestation of epilepsy and the MRI features had to remain constant over at least two MRIs within an interval of at least 12 months. Only in one patient (patient 10 with right-sided pDA) this interval was less than 12 months. In order to exclude high grade glial tumors there had to be no progression of the disease and no MRI contrast enhancement. Dysplastic tumors (ganglioglioma, GG and dysembrioplastic neuroepitelial tumor, DNT) were considered under pDA since they are incorporated in the classification of malformations of cortical development [21].

(3) Lesions other than AA or pDA.

The following rating scale was proposed, for size: 0 (normal), +1 (slightly enlarged), +2 (moderately enlarged), +3 (considerably enlarged), -1 (small), -2 (moderate atrophy), -3 (severe atrophy); for signal intensity: 0 (normal), 1 (moderately increased), 2 (considerably increased).

Agreement between the two raters (SB, GK) was reached in 23/25 cases (Cohen's kappa coefficient, $\kappa = 0.828$, $p < 0.0001$). Of these 23 patients, 15 could be classified as having normal amygdalae, 5 pDA, 2 AA, and one patient with other amygdalar lesion (a small cystic lesion adjacent to amygdala). In the remaining 2/25 cases, a third evaluator (ET, Department of Neurology, Innsbruck Medical University, Austria) was consulted. The decision was made with two out of three votes; there were no cases with three different rating scores. As a result of the assessment, 17 patients were classified as having normal amygdalae, 5 pDA, 2 AA and one other amygdalar lesion.

2.6. Statistics

Descriptive statistics were used for group comparisons due to the small sample size of the subgroups. Individual fMRI statistics were adopted based on multivariate models as provided by Brain Voyager QX.

3. Results

T2* contrast differences were found within amygdalae in all subjects but one in response to watching video sequences with fearful faces in contrast to watching landscape scenes ($p <$

0.05). The activation focus was located in the superior part of the amygdala, as found by Schacher *et al.* [17].

According to the criteria for the assessment of amygdalar structural abnormalities, 17 patients were classified as having normal amygdalae, five patients as having pDA, two as having AA, and in one patient a small cystic lesion adjacent to right amygdala was assessed.

Out of the 17 patients with normal amygdala, bilateral amygdalae activation was observed in three (18%) patients (mean LI -0.08), strongly lateralized right-sided activation in six (35%) (mean LI -0.72), strongly lateralized left-sided activation in seven (41%) patients (mean LI 1.00); and in one patient the activation was categorized as weakly lateralized to the left (LI 0.49).

In two patients with right-sided pDA, the activation was observed in the contralateral amygdala (for both LI 1) (Figure 1); whereas in three patients with left-sided pDA, activations were bilateral (n=1; LI -0.01), ipsilateral with strong lateralization (n=1; LI 0.82) or contralateral with strong lateralization (n=1; LI -0.67) (Figure 2).

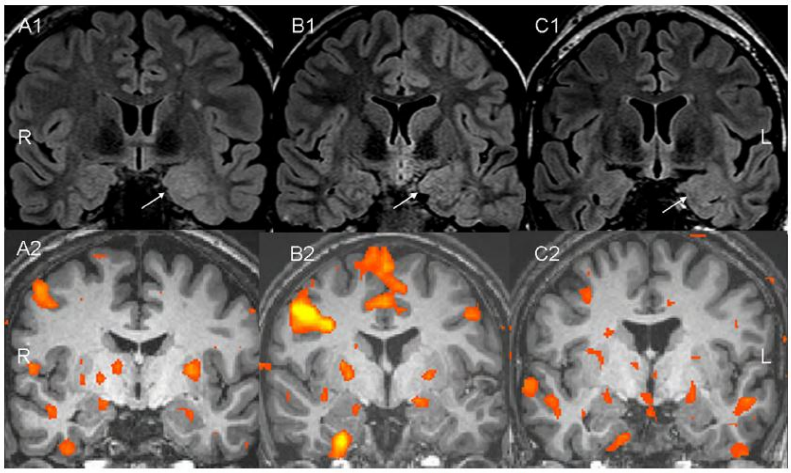

Fig. 1. Patients *N* correspond to the numbers indicated in Table 1. Upper row (A1 – patient N 21, B1 – patient N 25, C1 – patient N 22): coronal FLAIR (fluid attenuated inversion recovery) MRI images of three patients with left-sided amygdala dysplasia (white arrows). Amygdala has increased signal and is enlarged on the left side compared to the right; temporal lobe on the left is smaller and has increased signal in white matter. Lower row – patients with left-sided amygdala dysplasia: A2 (patient N 21) – fMRI BOLD-signal strongly lateralised to the right amygdala (LI –0.67); B2 (patient N 25) – fMRI BOLD-signal strongly lateralized to the left amygdala (LI 0.82); C2 (patient N 22) bilateral fMRI BOLD-signal in amygdala (LI –0.01). R – right; L – left.

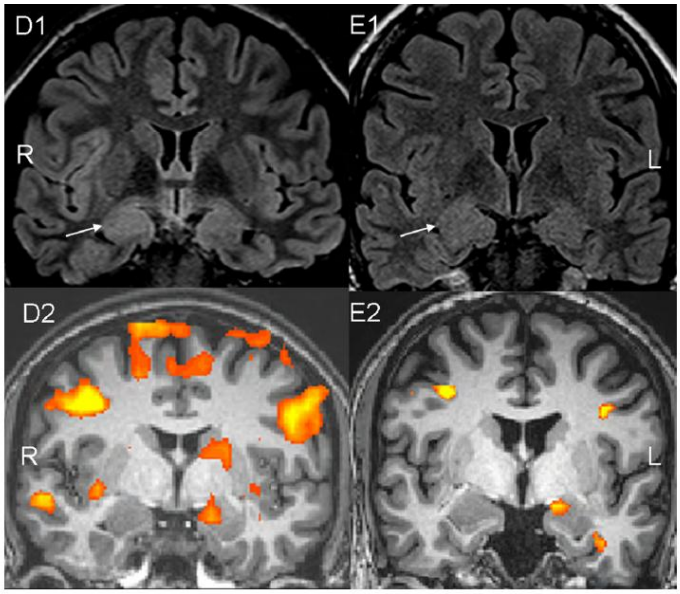

Fig. 2. Patients *N* correspond to the numbers indicated in Table 1. Upper row (D1 – patient N 8, E1 – patient N 10): coronal FLAIR (fluid attenuated inversion recovery) MRI images of two patients with right-sided amygdala dysplasia (white arrows). Amygdala has increased signal and is enlarged on the right side compared to the left. Lower row (D2 – patient N 8, E2 – patient N 10): strongly lateralised left-sided fMRI BOLD-signal, contralateral to dysplasia affecting right amygdala (LI for both cases 1). R – right; L – left.

In one patient with right-sided AA, the activation was observed ipsilateral with strong lateralization (LI -0.78), whereas in one patient with bilateral AA no activation was detected. In the patient with the small cystic lesion adjacent to the right amygdala, bilateral amygdala activation was observed (LI -0.13).

Across all subjects the average LI of amygdalar activation was 0.13 (SD 0.8).

In relation to the seizure onset side, amygdalar activation was contralateral in 15 (60%) patients (14/15 with strong lateralization) and ipsilateral in four (16%) patients (2/4 with strong lateralization). In two patients with left-sided TLE and in three patients with right-sided TLE, amygdalar activation was bilateral. No amygdalar activation was observed in one patient with bilateral mTLE and bilateral HS.

4. Discussion

We present a cohort of 25 consecutive pharmacoresistant TLE patients who were tested by means of an animated fearful faces paradigm that reliably elucidates amygdalar BOLD activation. A previous study has shown that this paradigm results in bilateral amygdalar activation in the majority of healthy controls, whereas the activation is mostly contralateral to the side of seizure onset in unilateral symptomatic TLE patients [17]. In our series we were able to reproduce the findings of our previous study [17] using an independent patient sample and a different scanner: the majority of patients (80 %) had activation contralateral to the side

of seizure onset. However, in four out of 25 symptomatic TLE patients, amygdalar activation was ipsilateral to mesial temporal lesion.

In this study, we aimed to investigate whether mesial temporal lesions observed on MRI could influence the activation pattern in the amygdala. Indeed, in two patients with left-sided pDA, significant activation was detected on the side of the lesion (activation was bilateral in one patient) demonstrating that unilateral pDA does not necessarily cause a loss of amygdalar function as indicated by fMRI BOLD-response. In contrast to these patients, two patients with right-sided and one with left-sided pDA showed strongly contralateral activation. Whether this apparent left right/asymmetry represents functional or structural differences as has been suggested remains speculative due to our small sample size [22, 23].

The histological type of dysplasia could also play an important role in the reactivity of pDA. It is not possible to determine the type of dysplasia based on MRI features since there are no correlative studies available with regard to amygdala imaging and histological features which would validate MRI characteristics of dysplasia affecting amygdalae. Few studies addressing cortical dysplasia (CD) function have demonstrated that phenotype, epileptogenicity and functional behavior of CD are largely determined by their cellular and histochemical properties. This has been shown mainly in invasive studies related to CD located in the vicinity of eloquent cortical regions [24]. Absence of language or motor functions in perirolandic and Broca's areas which exhibited histological evidence of CD with balloon cells (Palmini type IIb) and preservation of motor functions when balloon cells were absent (types Ia,b, IIa) was found in a study associating direct cortical stimulation and histology in CD [24]. The absence of function in CD type IIb may be due to immature properties of balloon cells, dysmorphic and cytomegalic neurons as well as severe disruption of neuronal circuits.

However, it is difficult to extrapolate the results obtained in CD to pDA since there is as yet very limited data available on amygdalar histology and functional imaging.

Constant MRI features over a relatively long time period, absence of swelling signs on initial MRI and of contrast enhancement and clinical presentation characteristic for other possible causes of amygdalar lesions (swelling, tumor, or inflammation) enabled us to categorize amygdalar lesion as probable dysplasia.

In patients with pharmacoresistant seizures a precise detection of the extent of an epileptogenic as well as functional deficit zone is essential for determining the resection borders in order to achieve seizure freedom without additional postoperative functional deficits [25]. In line with our previous study, we have demonstrated functional response in

amygdalae affected by epileptogenic lesions. Bonelli *et al.* [16] used a fearful face paradigm in mTLE patients for determining whether preoperative amygdalar response could be a potential predictive marker for emotional disturbances following surgery: greater increases in anxiety and depression were observed in patients who had greater preoperative amygdalar activations [16]. It is well established that psychosocial difficulties and psychiatric dysfunctions appear more often in patients with mTLE compared to other chronic epilepsy syndromes [26, 27].

Abnormalities in higher social cognition were found in both pre- and postoperative mTLE patients [28]. Based on the lesion and functional imaging studies, Kirsch [29] has highlighted the (among others) specific role of temporal lobe structures in social cognitive processes and indicated possible impairments in higher-order social behavior due to an anterior temporal lobectomy. However, another preliminary prospective study on social cognition did not reveal changes caused by anterior temporal lobectomy [30].

In summary, the results of this explorative study indicate that in TLE patients unilateral amygdala dysplasia does not necessarily cause a loss of amygdalar function as indicated by fMRI BOLD-response, but does frequently induce a shift of fMRI BOLD-signal to the contralateral side. However, for further delineation of response characteristics in dysplastic amygdala and its functional importance, a larger number of patients and pre- and postsurgical evaluations, including histopathology, are required.

Acknowledgements

We would like to thank the Swiss Epilepsy Foundation for financial support and Dr. Dominik Huber, Gesa Osterkamp, and Theresa Biesold for technical support. We also would like to thank Victoria Reed for valuable comments regarding the improvement of the manuscript.

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6 SUMMARY AND GENERAL DISCUSSION

The main purpose of this thesis was to investigate the relationship between MTLE, amygdala functioning and social cognition. The following key objectives were determined at the onset of the project:

- To assess emotion recognition, ToM, psychopathology and quality of life in MTLE patients
- To establish an association between ipsilateral amygdalar dysfunction in MTLE performance in ToM tasks, and lateralization of seizure-onset side
- To look for the association between ipsilateral amygdalar dysfunction in MTLE and functional connectivity of the amygdala with remote temporal and frontal brain areas
- To find out if there is an association between structural abnormalities and fMRI response in the amygdala in patients with TLE

In this final chapter the general findings of the studies are summarized according to these key objectives. Subsequently, the methodological considerations including the strengths and limitations of the studies are discussed and, finally, clinical implications and suggestions for future investigations are presented.

6.1 Summary

Emotion recognition, ToM, psychopathology and quality of life in symptomatic MTLE

This is the first study, which investigated emotion perception from faces and voices, theory of mind, decision-making abilities, and various aspects of psychopathology and quality of life using a battery of tests combining behavioural and psychological measures. For the diagnosis of the epilepsy syndromes, well-defined and rigorous diagnostic criteria were applied. Twenty-eight MTLE patients were compared with 14 extra-MTLE patients, and 29 HC on different measures of social cognition and psychopathology.

We hypothesized that patients with MTLE, compared to extra-MTLE patients and HC, are at increased risk for developing social-cognitive deficits. We found deficits in patients with MTLE compared to HC in all measures of social perception affecting the ability to interpret emotional expressions and feelings from faces and voices and, with one exception, on all ToM tests. Emotion recognition from expressions in voices was found to be most frequently

impaired, followed by the ability of subtle social reasoning as it is required in the faux pas test and the ability to use mental state terms to describe ToM animations. In contrast, in patients in whom mesio-temporal limbic and frontal structures were not involved, we did not find significant impairment in emotion recognition or ToM tests compared to HC, just as we did not find differences in performance compared to the MTLE group. Their performance lay between these two groups on most measures of social cognition.

We found that MTLE patients had deficits in decision making under conditions of ambiguity compared to HC, but not compared to extra-MTLE patients. While extra-MTLE patients and controls showed a significant learning effect over the blocks of the Iowa gambling task (IGT), MTLE patients' performance did not improve from the first to the last block of trials. Results suggest that epilepsy associated with brain abnormalities outside the temporal and frontal lobe structures do not have deleterious effects on decision making as is found for epilepsy caused by mesial temporal lobe pathologies. The present findings highlighted the specificity of the mesial temporal lobes in reward-based, adaptive learning and decision making. We did not find an overrepresentation of psychiatric symptoms in MTLE patients.

In general, no noticeable differences were found between patients with lateralization of their epilepsy in the left or right hemisphere. Furthermore, the association of social-cognitive deficits with several epilepsy-related variables was explored, and several modest positive associations were found especially between the degree of mental state attributions with age at epilepsy onset and duration of epilepsy. From these results it was concluded that patients with early epilepsy onset and longer duration of epilepsy are often more prone to develop ToM deficits.

In summary, MTLE can be considered a specific risk factor for developing deficits in emotion recognition, ToM and decision-making. It can be concluded that living with a chronic condition is an important factor predisposing these patients to social-cognitive deficits, but that brain dysfunction within the mesial temporal lobe structures can pose an additional hazard. Concomitant factors, such as amygdalar and frontal lobe dysfunction may play an additive role in developing social-cognitive deficits.

Association between ipsilateral amygdalar dysfunction in MTLE, performance in ToM abilities, and lateralization of seizure-onset side

Following the findings of the preceding investigations, the second study dealt with an intriguing aspect of MTLE, ToM, and its relation to the amygdala and therewith contrasting

behavioural and imaging measurements. Behavioural (neuropsychological) parameters are the indices of ToM, while fMRI-detected brain activation was an index of emotion (fear) perception. We hypothesized that amygdala activity induced by fearful face processing is associated with performance in a ToM task. We further explored the relationship between ToM abilities and the laterality of the epileptogenic zone and amygdala BOLD reactivity. In 31 patients with MTLE, we described a deficit in a ToM test that assesses the recognition of social faux pas, demonstrating poorer performances in patients with right-sided MTLE compared to patients with left-sided MTLE. In patients with right-sided MTLE, the recognition of faux pas scores correlated with the degree of asymmetry of fMRI activation in the ipsilateral amygdala consequent to fear-related stimuli. However, stepwise multiple regression analysis revealed that the amygdalar asymmetry ratio did not significantly contribute to the explanation of faux pas test performance variability beyond that explained by side of MTLE. We concluded from our finding that right-sided MTLE, not unilateral amygdala dysfunction per se, can be considered a risk factor for ToM deficits. Thus, our results lent support to right hemisphere specialization in higher-order social cognitive abilities.

Association between ipsilateral amygdalar dysfunction in MTLE and functional connectivity of the amygdala with remote temporal and frontal brain areas

The third study explored connectivity of the amygdala with different temporal, frontal, and parietal brain areas in patients with unilateral MTLE. The aim of this study was to evaluate whether ipsilateral amygdala dysfunction in unilateral temporal lobe epilepsy (MTLE) influences remote temporal, frontal, and parietal brain structures and to identify their association with ToM abilities. We hypothesized that MTLE patients show an altered amygdala network dependent on the lateralization of seizure-onset side due to deafferentiation. We further hypothesized that left- and right-sided MTLE patients show primarily impaired ipsilateral amygdala connectivity whereas contralateral amygdala connectivity should be less affected. In previous studies (Schacher, Haemmerle et al., 2006; Broicher et al., 2010) carried out by our group we were able to show that the animated fearful faces paradigm results in bilateral amygdalar activation in HC and lateralized amygdala activation contralaleral to the side of seizure onset in the majority of MTLE patients. In the present study, we were able to replicate and extend this finding, identifying symmetrical activation pattern within HC and a corresponding asymmetrical activation pattern within MTLE patients. The latter was not restricted to the amygdala, but could also be observed in

different frontal and temporal brain areas as well as subcortical structures of the brain. Our analysis of functional connectivity of the amygdala was based on this prior identification of a main effect of task in each study under investigation. We found an asymmetrical organized amygdala network within different temporal and frontal lobe brain structures in HC. In MTLE patients, we found a significant effect of lesion, whereby this effect of pathology was most prominent in brain areas showing greater connectivity. We did not find the expected impairment of ipsilateral connectivity in RMTLE patients, which suggests that despite only unilateral morphological MRI-proven pathology the contralateral hemisphere, may also be involved through transcallosal projections. We further investigated ToM performance in MTLE patients using the faux pas test and confirmed our previous finding that patients with MTLE, especially RMTLE, have deficits in the recognition of faux pas test. We conclude that a possible explanation for their poor performance may be that they had functional disturbances in both amygdalo-hippocampal areas compared to LMTLE patients who only were found only to have ipsilateral amygdalo-hippocampal dysfunction. Furthermore, in MTLE patients the extent of amygdalar connectivity to the parahippocampal gyrus and insula was related to ToM test performance. We concluded from our findings that ipsilateral amygdalar dysfunction is associated with alterations in remote temporal and frontal brain areas.

Association between structural abnormalities and fMRI response in the amygdala in patients with temporal lobe epilepsy

The assessment of the relationship between structure and function is essential in brain surgery for epilepsy and in predicting postoperative outcome. The fourth study was a first attempt to investigate whether amygdala reactivity is principally impaired if it is affected by dysplasia. Twenty-five patients with temporal lobe epilepsy (TLE) underwent fMRI testing with fearful face fMRI paradigm. We were able to replicate previously reported findings that the majority of patients (80%) with unilateral temporal lobe epilepsy (TLE) and hippocampal sclerosis (HS) show amygdala fMRI activations contralateral to the seizure onset side (Schacher, Haemmerle et al., 2006). The main aim of the study was to assess whether amygdala lesion observed on MRI could influence the activation pattern in the amygdala. We found that amygdala lesion is not necessarily associated with functional impairment, which was demonstrated in two patients with left-sided dysplasia from our series. The results indicate that the presence of BOLD-signal in fMRI does not necessarily exclude structural changes, while conversely the absence of a BOLD-signal is not inevitably indicative of

structural abnormalities. However, the results of the present study make it clear that prospective and longitudinal studies are necessary for a more differentiated perspective.

6.2 Methodological considerations

The methodological choices that were made concerning the inclusion of epilepsy patients are discussed below, including the instruments used to assess social cognition, psychopathology and quality of life and the role of amygdala fMRT in epileptology.

The first comment concerns the representativeness of the patient group that was investigated. For all four studies, the findings were based on patients who were admitted to the Swiss Epilepsy Centre in Zurich and the Department of Neurology at Innsbruck Medical University (only first study). The patients were hospitalized for several reasons, mainly because of preoperative evaluation, poor seizure control and change of anti-epileptic medication, but also for psychosocial evaluation and/or neuropsychological assessment. It may be assumed that all had a severe form of epilepsy. In all our studies exclusion criteria were an IQ below 75 (representing intellectual impairment) and psychiatric disorders except those with adjustment disorders and mild to moderate depression as it was assumed that these are comorbid symptoms of TLE. This may have led to an underestimation of psychopathology and impairments in quality of life in MTLE patients. Neuropsychological testing revealed no evidence of significant amnesia, agnosia, aphasia, apraxia, alexia, or agraphia in any of the patients. Only patients who had mild to moderate impairments in the domains of attention, executive function, and episodic memory were included in the studies. Moreover, all studies had relatively small sample sizes. Therefore, it remains to be established whether the present study results can be generalized to the total population of MTLE patients. Furthermore, the majority of MTLE patients in our studies had unilateral hippocampal sclerosis, representing a relatively homogenous patient group, whereas in our first study, described in section 5.1, there were also a few patients who had other lesions within the medial temporal lobe (e.g. parahippocampal gyrus, amgygdala). We also excluded patients with the diagnosis of frontal lobe epilepsy because of the assumed role of frontal lobe function in social cognition. Future studies should be directed at investigating social cognition in different subgroups (based on different clinical characteristics: e.g. amygdalar pathology, pre- and postoperatively, side of lesion) of MTLE patients and frontal lobe epilepsy patients.

The second point of concern are the diagnostic instruments that were employed in our first study for investigating social cognition and psychopathology. We employed the most commonly utilized or representative tests of social cognition as well as reliable and widely applied self-report questionnaires of psychopathology.

Emotional processing was assessed with the Comprehensive Affect Testing System (CATS), which is a computerized measure of the visual and auditory emotional processing of the six basic emotions. Instructions and verbal and auditory stimuli for the CATS task were translated by our group into German. Currently, no normative data are available for the German version of the CATS. Although this test has not been widely used in either clinical or research settings, data collection is in progress with different groups of patients with brain damage. The short version of the "Recognition of Faux Pas Test" was assembled from 34 subjects who completed the full version. Stories that did not show a sufficient amount of interindividual variability and resulted in ambiguous answers were eliminated. Reliability analysis between the long and the short version in this sample revealed a sufficient correlation between the two versions. We also used a shortened version of the "Reading the Mind in the Eyes Test" that comprised ten selected pair of eyes which was assembled from an independent sample of 20 healthy subjects who completed the full version. Reliability of the shortened German translation was good. The "Moving Triangles Test", a measure of the extent to which subjects make mental state attributions to dynamic visual stimuli, was also translated into German. Quality of life was studied with an instrument that was specifically developed for patients with epilepsy, namely the Quality of Life with Epilepsy-31 (QUOLIE-31). This inventory, that evaluates seven areas of quality of life, was translated into German and the psychometric properties were determined. Just as for the original English version, the factor structure, reliability and validity were good which makes the short version a suitable instrument to investigate quality of life in epilepsy patients. For the study described in section 5.1, in addition to the instruments described above, we also used several other reliable and widely used self-report-questionnaires.

The final point concerns the role of amygdala fMRI in epileptology. fMRI is increasingly applied in presurgical evaluation of refractory epilepsy patients. The goal of epilepsy surgery is a complete resection of the epileptogenic zone without a postoperative neurological deficit. fMRI is a good marker for functional assessment of mesial temporal structures and the amygdala in particular: it provides information about the functional integrity of a brain structure that could not be obtained through anatomical imaging.

Altogether, there is an increase of findings that identify and characterize a plenitude of relevant influencing factors that modulate amygdala activity. According to two independent meta-analytic reviews of imaging studies published by Costafreda et al. (2008) and Lindquist et al. (Lindquist, 2011), the probability of finding amygdala activation is highest in perception of fear as compared to the perception of any other emotion category. Moreover, we used dynamic as opposed to static fearful stimuli, which were demonstrated to more reliably recruit neural networks of emotion (van der Gaag, Minderaa, & Keysers, 2007).

The feasibility of imaging the amygdala individually permits the evaluation of possible clinical implications of amygdala resections. In our patients we can only compare the ipsi- with the contralateral side and not the absolute amygdalar fMRI BOLD signal, which becomes problematic in patients with bilateral pathologies. In our second study (section 5.2) we therefore used an asymmetry score and correlated it with the recognition of faux pas test results. Since the size of the absolute fMRI BOLD signal demonstrates a very large interindividual variability due to anatomical, vascular, and psychophysical factors in general and is additionally modulated by medication in epilepsy patients, we applied an asymmetry ratio as used in previous publications (Schacher, Haemmerle et al., 2006). An asymmetry ratio reflects lateralized pathology and integrity in patients with lateralized pathology and is therefore reasonably related to behavioural measures under assumption of bilateral symmetrical representation of function in HC. Unfortunately, we cannot provide information about the correlation of asymmetry ratio and faux pas test performance in healthy volunteers.

Since one main limitation in the second and third study of this thesis was the temporally independent measurements of amygdala activity and behavioural test performance, future studies should try to overcome this limitation.

6.3 Strengths and limitations of the present studies

This is the first study on social cognition in MTLE patients that has used a comprehensive battery of social-cognitive and psychiatric instruments in order to determine in more detail the deficits in social cognition and psychiatric symptoms that have been previously noted in these patients. We used the most commonly used or representative tests of emotion recognition, ToM, and decision-making as well as reliable and valid diagnostic instruments of psychopathology aimed at determining the specific nature of impairments in social cognition.

It is well established that MTLE patients, as compared to healthy controls, often suffer from cognitive dysfunctions. These deficits concern verbal or visual memory, but also executive functions that may critically influence social and/or emotional processing. We did

not report detailed neuropsychological tests in our studies. To evaluate the interaction of cognitive, social and emotional dysfunction, more detailed data would be necessary. This concern all studies of this thesis, since activation in the amygdala may also correlate with other cognitive functions or with depression that may lead to deficits in social cognition. However, we therefore included only patients who had mild to moderate impairments in the domains of attention, executive function, and episodic memory and excluded patients with psychiatric disorders except those with adjustment disorders and mild to moderate depression.

We also used control groups to compare our findings, except in our second study (section 5.2) in which neither a healthy nor a clinical control group was included. In our first study (section 5.1) performance of MTLE patients was compared to that of patients with epilepsies originating outside the temporal and frontal lobe structures (extra-MTLE) and "healthy" controls. The groups were homogenous in terms of several demographic and clinical characteristics. However, our clinical control group was composed of patients affected by different epilepsy syndromes and a more homogenous control group should be considered in future studies.

6.4 Clinical implications

The findings of this thesis show that deficits in social cognition seem to be a defining symptom of MTLE that may have important implications for the development, course, and outcome of this illness. When treating patients with MTLE one should keep in mind that these deficits frequently co-exist and sometimes may even be more disruptive than the epilepsy itself. Furthermore, our findings showed only a small number of modest associations between ToM performance and epilepsy-related variables, notably, age at epilepsy onset and duration of epilepsy (e.g. patients with earlier epilepsy onset and longer duration of epilepsy are more prone to have deficits in ToM). From a clinical point of view, it means that there are no epilepsy variables that can be considered as strong predictors (risk factors) for the development of social cognitive deficits within the group of MTLE patients. Yet, aspects of social cognition are not often part of the psychiatric or neuropsychological assessment of patients with epilepsies. We strongly recommend the expansion of cognitive assessment batteries to include tests of social cognition. Tests that show promising results should be available to clinicians and should be normed on samples that are large enough to establish sound reliability and validity data. Since social-cognitive skills may be associated with social functioning, intervention may be devised to ameliorate them, which, in turn, may have a concomitant impact on long-term outcome.

The feasibility of imaging the amygdala individually permits the evaluation of possible clinical implications of amygdala resections. Patients who sustain surgical damage to a presurgically normal amygdala or patients with dysfunctions of the remaining amygdala on the contralateral side of the seizure onset could be at risk for impairments in their emotional and social processing. Functional connectivity analysis may improve our understanding of the local and remote impacts of the epileptogenic lesion on pathways and networks. Whether this information will be useful in predicting deficits following epilepsy surgery is unknown.

6.5 Suggestions for future studies

The findings of the different studies that are part of this dissertation strongly suggest that MTLE can be considered a specific risk factor for developing social-cognitive deficits. Since patients with epilepsies not originating from the medial temporal lobes may also be at risk, even though to a lesser degree, the psychosocial impact of having a chronic epileptic condition should not be underestimated and be more integrated in future studies on social cognition in epilepsy. Furthermore, the study design can be further improved when a control group of other chronic medical patients in addition to the epilepsy patients is included in the investigation. To increase ecological validity, the use of dynamic and multimodal information is recommended to present more "real-life" situations. Furthermore, conducting controlled naturalistic studies may help to find out how these social-cognitive impairments affect patient's personal and professional life and therewith also their quality of life.

An impressive body of knowledge is accumulating on the roles of individual regions of the brain, such as the amygdala, in social cognition. However there is less consistency and little hard empirical data about the detailed interactions of these regions as part of a broader social-cognitive brain system. Since the entire network of emotions is essential to intact emotional experiences and social behaviour, neuroimaging research into psychiatric and neurological disorders in which affective symptoms and deficits in social cognition manifest more frequently, may help to advance our understanding of the brain-behaviour relationship. Functional connectivity analysis of fMRI data may provide novel insights for identifying effective and functional connectivity between cerebral areas involved in social-cognitive networks and the structural basis of this. However, continued active research is required to translate advances in neuroimaging, such as fMRI connectivity analysis, into clinical practice and thus into improved outcomes for patients.

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7 PUBLICATIONS

7.1 Papers

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7.2 Book chapter

Broicher, S.D. and Jokeit, H. Emotional agnosis and theory of mind. In: The Neuropsychiatry of Epilepsy: A functional analysis (Ed M. R. Trimble). Cambridge University Press, 2011.

7.3 Posters

Burckhardt, R., **Broicher, S.D.**, Ebner, A., Pannek, H., Yonekawa, Y., Grunwald, T., Krämer, G., Kurthen, M. and Jokeit, H. (2009). Verbal semantic processing after language dominant anterior temporal lobe resection versus transsylvian selective amygdalo-hippocampectomy. Poster presented at the ZNZ Symposium 2010, Zurich, Switzerland.

Burckhardt, R., **Broicher, S.D.**, Ebner, A., Pannek, H., Yonekawa, Y., Grunwald, T., Krämer, G., Kurthen, M. and Jokeit, H. (2009). Verbal semantic processing after language dominant anterior temporal lobe resection versus transsylvian selective amygdalo-hippocampectomy. Posterpräsentation an der 6. gemeinsamen Jahrestagung der

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Broicher, S.D., Arter, F., Grunwald, T., Huber, D., Kurthen, M., Krämer, G. and Jokeit, H. (2010). Amygdalar fMRI response is related to advanced social cognition in patients with unilateral mesial temporal lobe epilepsy. Poster presented at the ZNZ Symposium 2010, Zurich, Switzerland.

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Broicher, S.D., Frings, L., Huppertz, H.-J., Grunwald, T., Kurthen, M., Krämer, G. and Jokeit, H. (2011). Alterations in functional connectivity of the amygdala in unilateral mesial temporal lobe epilepsy. *Journal of Neurology*,DOI10.1007/s00415-012-6533-3.

7.4 Talks

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Broicher, S.D. (2011). Mapping Emotion. Vortrag an der 7. Gemeinsamen Jahrestagung der deutschen, österreichischen und schweizerischen Liga gegen Epilepsie, Graz, Österreich.

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Broicher, S.D. (2011). Soziale Kognition bei Epilepsie. Vortrag am Herbstsymposium des Schweizerischen Epilepsie-Zentrums, Zürich, Schweiz.

8 CURRICULUM VITAE

PERSONAL DATA

Date of Birth:	01.05.1983
Place of Birth:	Rinteln, Germany
Nationality:	German

EDUCATION

02/2012-today	**Psychiatric University Hospital Zurich** Division of Psychiatry Research & Psychogeriatric Medicine Neuropsychologist Prof. Dr. Christoph Hock
10/2008-01/2012	**University of Zurich** Thesis at the Swiss Epilepsy Centre, Department of Neuropsychology Prof. Dr. rer. nat. Hennric Jokeit Research Area: „Social cognition in patients with frontal and temporal lobe epilepsies" Disputation 03/12 with *Summa cum laude*
10/2011-11/2011	**University of California San Francisco (UCSF)** Visiting Scholar at the Memory and Aging Center (MAC) Prof. Dr. Katherine Rankin Research Area: „Social cognition in frontotemporal dementia"
10/2008-09/2011	**University of Zurich and ETH** International PhD Programm at the Center of Neuroscience Zurich (ZNZ)
08/2007-06/2008	**University of Bern** Masterthesis at the Institute of Psychology in Bern, Department of Neuropsychology Prof. Dr. Katharina Henke Research Area: „Resilience and longevity of unconsciously acquired memory traces"
10/2006-10/2008	**University of Bern** Master of Science in Psychology
10/2003-09/2006	**University of Fribourg**

	Bachelor of Science in Psychology (Neuroscience)
07/1997-06/2002	**Kurt-Schwitters-Gymnasium, Hannover** Abitur
07/1995-06/1997	**Gymnasium Ernestinum, Rinteln**